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The College on Problems of Drug Dependence, Inc.

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Problems of Drug Dependence 2006:
Proceedings of the 68th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc.

Editor:

William L. Dewey, Ph.D.
Virginia Commonwealth University

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Strain differences in reinforced and non-reinforced responding for cocaine

T. A. Kosten, X. Y. Zhang and C. N. Haile, Yale University School of Medicine, West Haven, CT

Dose-related attenuation of cocaine and food reinforcement following pretreatment with tacrine K. W. Grasing(1,2), S. He(1) and R. Moreno(1), (1) VA Medical Center, Kansas City, MO and (2) University of Kansas Medical Center, Kansas City, KS

Effects of progesterone and estrogen on reinstatement of cocaine-seeking behavior in female rats
J.J. Anker, E.B. Larson and M.E. Carroll, University of Minnesota, Minneapolis, MN

Reinstatement of cocaine-seeking behavior in rats selected for high or low impulsivity or saccharin intake: Sex differences
J. L. Perry, S. E. Nelson, J. J. Anker and M. E. Carroll, University of Minnesota, Minneapolis, MN

Comparison of FR1 and VR5 reinforcement schedules during self-administration training and subsequent cue reinstatement testing of cocaine-seeking behavior
K. J. Thiel, J. I. Acosta, J. R. Browning, J. M. Wenzel and J. L. Neisewander, Arizona State University, Tempe, AZ

Gabapentin has no effect on cocaine-primed relapse and cocaine-induced increases in dopamine in the nucleus accumbens
X. Li, Z. Xi, X. Peng, J. Gilbert, A. Pak and E. Gardner, NIDA Intramural Research Program, Baltimore, MD

Effects of NMDA and NMDA antagonists on cocaine-associated conditioned reinforcer-induced reinstatement in rats
P.M. Beardsley and J.L. Newman, University of Minnesota, Minneapolis, MN and Virginia Commonwealth University, Richmond, VA

Behavioral effects of cocaine in rats are enhanced by stromal cell derived factor 1 (SDF-1)
J. Trecki and E. M. Unterwald, Temple University School of Medicine, Philadelphia, PA

Intra-accumbal Tat (1 – 72) attenuates IV cocaine-induced locomotor activity in rats: Role for D1 receptors in cocaine/Tat-induced neurotoxicity?
S. B. Harrod, C. F. Mactutus, J. Silvers, M. Aksenova, S. Fitting, U. Hasselrot, M. Aksenov and R. M. Booze, University of South Carolina, Columbia, SC

Comparisons of the in vitro binding of [3H]WIN 354,428 with [3H]JHW 007, a dopamine transporter ligand that blocks the effects of cocaine
T. A. Kopajtic(1), A. H. Newman(2) and J. L. Katz(1), (1) Psychobiology Section, and (2) Medicinal Chemistry Section, NIDA Intramural Research Program, Baltimore, MD

A single exposure to cocaine produces withdrawal-associated increases In 5-HT2A serotonin receptor function in rats
G. Battaglia, H. Rosczyk and G.A. Carrasco, Loyola University Chicago, Maywood, IL

Opposite effect on rat lateral hypothalamic orexin mRNA levels by morphine withdrawal and by chronic "binge" cocaine or withdrawal from cocaine CPP
Y. Zhou(1), C. L. Cui(2), M. Randesi(1), A. Ho(1), J. S. Han(2) and M. J. Kreek(1), (1) The Rockefeller University, New York, NY and (2) McLean Hospital, Harvard Medical School, Boston, MA

Phosphorylation of Akt is decreased in the nucleus accumbens of rats treated acutely with cocaine in a binge-pattern
S. A. Perrine, M. R. McCafferty and E. M. Unterwald, Temple University School of Medicine, Philadelphia, PA

Amphetamine, but not cocaine, attenuates Akt activity in hDAT-expressing cells and striatal synaptosomes
A. Galli(2), Y. Wei(2), J. M. Williams(2), J. A. Javitch(3) and C. Saunders(1), (1,2) Vanderbilt University Medical Center, Nashville, TN and (3) Center for Molecular Recognition, College of Physicians and Surgeons, Columbia University, New York, NY

Persistent changes in medial prefrontal cortex mRNA levels following binge cocaine self-administration and varying durations of abstinence
D. Morgan(1), W. M. Freeman(2), K. Patel(2), L. Thomas(3), K. E. Vrana(2) and D. C. Roberts(3), (1) University of Florida College of Medicine, Gainesville, FL, (2) Pennsylvania State University, Hershey, PA and (3) Wake Forest University School of Medicine, Winston-Salem, NC

Co-expression of glutamate AMPA receptor subunits and fos protein expression elicited by cocaine cues in rats
A. R. Zavala(1), S. Biswas(1), R. E. Harlan(2) and J. L. Neisewander(1), (1) Arizona State University, Tempe, AZ and (2) Tulane University School of Medicine, New Orleans, LA

CRAVING

Enhanced sensitivity to stress and drug craving in abstinent cocaine-dependent individuals compared to matched control volunteers
R. Sinha, H. C. Fox, K. Kemp and K. M. Siedlarz, Yale University, New Haven, CT

The effects of stress imagery on the subjective measures of craving and mood in methamphetamine-addicted volunteers

L. Harrison, R. De La Garza, II, C. Hurley, S. E. Evans, G. Fleury, V. Boss-Edwards and T. F. Newton, David Geffen School of Medicine at UCLA, Los Angeles, CA

Methamphetamine- or cocaine-induced craving: Cause or consequence of frequent drug use?

T. F. Newton, R. De La Garza, II, and A. D. Kalechstein, David Geffen School of Medicine at UCLA, Los Angeles, CA

Psychometric properties of the cocaine craving questionnaire (Long and Brief) and relationship to cocaine relapse outcomes

P. Paliwal, J. Sleeper, K. Kemp and R. Sinha, Yale School of Medicine, New Haven, CT

Cocaine craving early in residential treatment as predictor of treatment attrition and cocaine use outcomes

D. J. Rohsenow(1,2), R. A. Martin(1), C. A. Eaton(1) and P. M. Monti(1,2), (1) Brown University and (2) VA Medical Center, Providence, RI

POLYDRUG ABUSE I

Youth Latino immigrant population and drug use in leisure areas

S. Tortajajada(1), V. Agullo(1), M. Castellano(2), J. Valderrama(1), R. Aleixandre(1), J. Perez(3) and P. Needle(4), (1) Instituto de Historia de la Ciencia y Documentacion, and (2) Conselleria Sanitat, Generalitat Valenciana, Valencia, Spain, (3) Hospital Sant Pau, Barcelona, Spain and (4) Consultant to NIDA, Atlanta, GA

Concurrent use of heroin with other drugs among young never-injecting heroin users in Puerto Rico

H. M. Colon, H. A. Finlinson and R. R. Robles, Center for Addiction Studies, School of Medicine, Universidad Central del Caribe, Bayamon, Puerto Rico

Colombia 2003: Drug involvement of school-attending youths in Ibagué, Colombia

M. I. Gutierrez, V. H. Munoz, R. Espinosa, E. Munoz and A. La Torre, Universidad del Valle, Cali, Valle, Colombia

Drug use and ethnic identity among recent immigrants to the US of Hispanic origin

F. A. Wagner(1), C. Eith(2) and D. C. Browne(1), (1) Morgan State University, and (2) Towson University, MD

The US border in context: How does drug use compare?

L. Wallisch and R. Spence, University of Texas, Austin, TX

Drug use and the DAST-10: Differences among collegiate sexual minority women

W.B. Bostwick(1), S. McCabe(1), M. Grey(3), J. Cranford(1) and C. Boyd(2), (1) Substance Abuse Research Center, and (2) Institute for Research on Women and Gender, University of Michigan, Ann Arbor, and (3) Eastern Michigan University, Ypsilanti, MI

Drug and alcohol intoxication in violent victimizations on the Southern Ute Indian reservation

J. C. Abril, Medical and Health Research/National Development and Research Institutes, New York, NY

Years of potential life lost and mortality among California drug abusers in treatment

J. Fan and Y. I. Hser, NPI, Integrated Substance Abuse Program, UCLA, Los Angeles, CA

Racial/ethnic disparities and duration of drug use disorders

I. Kuo and H. D. Chilcoat, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Predictors of youth substance use in substance-abusing families

M. E. Burstein(1), C. Stanger(2) and J. Kamon(1), (1) University of Vermont, Burlington, VT and (2) University of Arkansas for Medical Sciences, Little Rock, AR

Mixed outcomes from brief substance use interventions with homeless adolescents

J. S. Baer(1), P. L. Peterson(3), E. A. Wells(2) and S. B. Garrett(3), (1) Department of Psychology, (2) School of Social Work, and (3) Alcohol and Drug Abuse Institute, University of Washington, Seattle, WA

Social support and substance abuse treatment service use in a homeless drug-abusing population

K. M. Eyrich(1), D. E. Pollio(2) and C. S. North(3), (1) Temple University, Philadelphia, PA, (2) Washington University, St. Louis, MO and (3) University of Texas Southwestern Medical Center, Dallas, TX

Service needs, utilization, and outcomes of women in women-only and mixed-gender drug abuse treatment programs

N. Niv and Y. I. Hser, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Assessing organizational needs and readiness for innovation training

G. A. Rowan-Szal, G. Joe, J. Greener and D. D. Simpson, Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

Early treatment evaluation as predictor of proximal and distal post-treatment recovery outcomes

V. Stanick(1), A. Laudet(1), J. Carway(2) and B. Sands(3), (1) National Development and Research Institutes, (2) VIP, and (3) NYC-HHC, NewYork, NY

Three-year patterns of 12-Step attendance and involvement as predictors of stable recovery from polydrug use
A. B. Laudet(1), W. White(2) and G. Storey(3), (1) National Development and Research Institutes, New York City, NY, (2) Chestnut Health Systems, Bloomington, IL and (3) SHARC, Melbourne, Victoria, Australia

Life meaning as potential mediator of 12-Step participation benefits on stable recovery from polysubstance use
W. White(1) and A. Laudet(2), (1) Chestnut Health Systems, Bloomington, IL and (2) National Development and Research Institutes, New York, NY

The role of on-site 12-Step meeting during treatment as a predictor of future 12-Step attendance and support for abstinence
K. J. Morgen(1), A. Laudet(1), V. Stanick(1), J. Carway(2) and B. Sands(3), (1) National Development and Research Institutes, (2) VIP Community Services, and (3) Woodhull Medical Center, New York, NY

Is this urine really clean? Adulteration in urine drug screening and testing
W. Jaffee(1), E. Trucco(1), C. Teter(2), S. Levy(3) and R. Weiss(1), (1) Alcohol and Drug Abuse Treatment Program, Harvard Medical School/McLean Hospital, Belmont, MA, (2) Bouve College of Health Sciences, Northeastern University, and (3) Center for Adolescent Substance Abuse Research, Harvard Medical School/Children's Hospital, Boston, MA

Sildenalfil use by veterans in substance abuse treatment
R. M. Guerra(1), K. Horvath(1), D. A. Calsyn(1,2), C. A. Malte(1) and A. J. Saxon(1,2), (1) Veterans Affairs Puget Sound HCS, and (2) University of Washington, Seattle, WA

Effects of cognitive-behavioral stress management on stress reactivity in substance-dependent individuals: A pilot study
S. E. Back, K. T. Brady, S. Gentilin, L. M. Jenkins and K. L. Brooks, Medical University of South Carolina, Charleston, SC

OPIATES: TREATMENT I

Cognitive deficits of opiate-dependent individuals entering methadone maintenance and brief cognitive-behavioral treatment
M. C. Chawarski and R. S. Schottenfeld, Yale University, New Haven, CT

Psycho-physiologic reactivity and cortisol levels in methadone- or buprenorphine-maintained patients and non-dependent controls in response to cue exposure
Z. Massida, M. Verger, M. Fatseas, E. Lavie, C. Denis, P. Franques-Reneric and M. Auriacombe, Universite Victor Segalen Bordeaux 2, Bordeaux Cedex, France

Respiratory depression during methadone induction
J. M. White, E. B. Morton, D. J. Foster, F. Bochner and A. A. Somogyi, University of Adelaide, Adelaide, South Australia, Australia

Characteristics of overweight long-term narcotic users
E. Evans, J. Fan and Y. Hser, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Weight and other cardiovascular risk factors increase during methadone treatment
A. Umbricht, L. Nanda, M. R. Lofwall and G. E. Bigelow, Johns Hopkins University School of Medicine, Baltimore, MD

Clinical correlates of accelerated aging: Multiple stem cell lineage depression in addiction
M. Missenden and A. S. Reece, General Practice, South City Medical Centre, Brisbane, Queensland, Australia

Risk for opioid abuse/dependence in non-medical prescription opioid users: Evaluating the role of gender
R. Desai, L. Sullivan, W. Becker, J. Tetrault and D. Fiellin, Yale University, New Haven, CT

Pilot study to reduce cigarette smoking among methadone patients
K. E. Dunn, S. C. Sigmon and S. T. Higgins, University of Vermont, Burlington, VT

Encouraging adoption of methadone medical maintenance: A technology transfer study
V. L. King(1), C. Burke(1), M. Kidorf(1), K. Stoller(1), R. Schwartz(2) and R. Brooner(1), (1) Johns Hopkins School of Medicine, and (2) Open Society Institute, Baltimore, MD

Methadone maintenance patients in the therapeutic community: Preliminary results
J. L. Sorensen(1), S. Andrews(1), N. Haug(1), M. Spencer(2), J. Guydish(1), K. Delucchi(1) and C. Masson(1), (1) University of California, and (2) Walden House, Inc., San Francisco, CA

Relationships between religious coping, perceived health, and methadone maintenance treatment outcomes
I. Cohen(1), E. Peles(1), M. Adelson(1) and Y. Benyamini(2), (1) Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel and (2) Tel-Aviv University, Ramat-Aviv, Israel

Buprenorphine versus methadone maintenance treatment: Predictors of treatment retention
R. P. Mattick(1), R. Ali(3), J. White(2), S. O'Brien(1) and J. Bell(1,4), (1) University of New South Wales, Sydney, (2)Adelaide University, (3) SA Department of Health, Adelaide, South Australia, and (4) NSW Department of Health, Sydney, New South Wales, Australia

Buprenorphine awareness and avoidance among street heroin users in NYC

B. D. Johnson, W. R. Davis, S. J. Sifaneck and E. Dunlap, Special Populations Research, National Development and Research Institutes, New York, NY

The role of ancillary meds in treatment with buprenorphine

W. Ling, M. P. Hillhouse, C. P. Domier and The CTN Buprenorphine Study Protocol Group, Integrated Substance Abuse Programs, University of California, Los Angeles, CA

Buprenorphine and bupropion combination for opioid-dependent smokers

M. Sofuoglu(1), M. Mooney(2), G. Gonzalez(1), K. Gonsai(1), J. Poling(1) and T. Kosten(1), (1) Yale University, New Haven, CT and (2) UCSF, San Francisco, CA

Effective buprenorphine tapering: Research findings to guide practice

C. M. Thomas(1,2), J. Annon(1), J. Fradis(1,2), A. Saxon(3), W. Ling(1) and * CTN Buprenorphine Study Group(4), (1) UCLA Integrated Substance Abuse Programs, and, (2) Friends Research Institute, Los Angeles, CA; (3) VA Puget Sound Health Care System, Seattle, WA and (4) NIDA CTN, Bethesda, MD

Clinician adherence to counseling manuals during office-based buprenorphine maintenance

M. V. Pantalon(1,2), D. A. Fiellin(1), M. C. Chawarski(1,2), M. E. Lavery(1), D. T. Barry (1,2), B. A. Moore(1,2), P. G. O'Connor(1) and R. S. Schottenfeld(1,2), (1) Yale University School of Medicine, and (2) The APT Foundation, Inc., New Haven, CT

Facilitating buprenorphine implementation: The Physician Clinical Support System

J. Egan(2), J. Netherland(2), R. Finkelstein(2) and D. Fiellin(1), (1) Yale University, New Haven, CT and (2) New York Academy of Medicine, New York, NY

The Clinical Trials Network and treatment innovations: Differences in counselor attitudes toward buprenorphine

H. Knudsen, L. J. Ducharme, P. M. Roman and J. A. Johnson, Institute for Behavioral Research, University of Georgia, Athens, GA

Minimal vs. enhanced counseling and directly observed therapy in primary care buprenorphine treatment

D. Fiellin, D. Barry, B. Moore, M. Chawarski, L. Sullivan, P. O'Connor and R. Schottenfeld, Yale University School of Medicine, New Haven, CT

HIV/AIDS I

Access to hepatitis treatment and risk behaviors among disenfranchised drug users from Rio de Janeiro, Brazil

M. Malta(1), F. Bastos(1), S. Cavalcanti(2), E. Massard(1), N. Bertoni(1), M. Hacker(1), E. Adlaf(3) and L. Gliksman(3), (1) Fiocruz, and, (2) Senad, Rio de Janeiro, Brazil; and (3) CAMH, Toronto, Ontario, Canada

Risk behavior study among heroin abusers in Wuhan, China

G. Jie(1), W. Ho(2), D. Zhou(1) and D. Metzger(2), (1) Wuhan Center for Disease Prevention & Control, Wuhan, China and (2) the University of Pennsylvania School of Medicine, Philadelphia, PA

HIV prevalence among injection drug users in Vinnitsya, Ukraine

K. Dumchev(1), R. Soldyshev(2), J. Schumacher(3), L. Moroz(2) and O. Zezyulin(1), (1) Vinnitsya Regional Narcological Dispensary, and (2) Vinnitsya Pirogov Medical University, Vinnitsya, Ukraine; and (3) University of Alabama at Birmingham, Birmingham, AL

Hormone injection among persons who transform their gender

L. A. Nuttbrock, S. Wahng and A. Rosenblum, Institute for Treatment and Services Research, National Development and Research Institutes, New York, NY

Gender differences between out-of-treatment injectors

D. Rinehart, C. F. Kwiatkowski, K. F. Corsi and R. E. Booth, University of Colorado at Denver and Health Sciences, Denver, CO

Methamphetamine injectors compared to other IDUs in Denver, CO

K. F. Corsi, C. F. Kwiatkowski and R. E. Booth, University of Colorado School of Medicine, Denver, CO

Gender differences in rates of positive urine drug tests for opiate, cocaine, and marijuana use among South African drug users

A. Moleko(2), W. W. Latimer(1), J. Towers(1), C. Maroga(2), F. Mantlwa(2) and S. Molonyane(2), (1) Johns Hopkins Bloomberg School of Public Health, Baltimore, MD and (2) University of Pretoria, Pretoria, South Africa

Rates of positive drug test screens of opiate, cocaine and marijuana use among urban African- American and White drug users

S. Bell, K. Drews, J. Rose and W.W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Medication adherence among HIV-positive methadone patients: Analysis of a new statistical tool

G. J. Knafl(1), K. L. Delucchi(2,3), N. Haug(2) and J. Sorensen(2), (1) School of Nursing, Oregon Health and Science University, Portland, OR, (2) Department of Psychiatry and (3) Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

The impact of self-efficacy, medication attitudes, and substance abuse on HIV medication adherence
G. Marzani-Nissen(1), K. S. Ingersoll(1), J. X. Cohen(3) and C. J. Heckman(2), (1) University of Virginia, Charlottesville, VA, (2) Virginia Commonwealth University, Richmond, VA and (3) University of California Santa Barbara, Santa Barbara, CA

The helping alliance in a motivational intervention to reduce cocaine use and increase HIV medication adherence
S. D. Ceperich(1), K. S. Ingersoll(1) and C. C. Wagner(2), (1) University of Virginia, Charlottesville, and (2) Virginia Commonwealth University, Richmond, VA

The choice for rapid HIV testing among drug users within HIV prevention
C. McCoy, M. Comerford, L. Metsch and S. T. Comerford, University of Miami, Miami, FL

Gender differences in improvement in readiness to change crack cocaine use: Comparing pee-enhanced versus standard HIV prevention interventions
A. V. Schlosser, S. Bradford, C. Callahan and L. Cottler, Washington University School of Medicine, St. Louis, MO

HIV risk reduction for migrant drug users: MMTP clients conducting peer outreach
S. Deren, S. Kang, M. Mino and H. Guarino, Institute for AIDS Research, National Development and Research Institutes, New York, NY

Examining the potency of a community-friendly HIV risk-reduction intervention
M. Copenhaver(1), I. Lee(1) and A. Margolin(2), (1) University of Connecticut, Storrs, and (2) Yale University School of Medicine, New Haven, CT

Drug-using network contributions to HIV risk among substance abusers entering methadone treatment
R. Bluthenthal(1,2), N. Forge(1), E. Wong(3), S. Chien(1) and M.Y. Iguchi(1,4), (1) Health & DPRC, RAND, Santa Monica, (2) Charles R. Drew University, Los Angeles, (2) Integrated Substance Abuse Research Program, and (4) University of California Los Angeles, Los Angeles, CA

HCV service awareness among drug treatment staff: Program barriers to clients' optimal utilization of HCV services
J. Astone-Twerell, S. Strauss, C. Munoz-Plaza, D.C. Des Jarlais, M. Gwadz, H. Hagan, A. Osborne and A. Rosenblum, National Development and Research Institutes, Inc., and Beth Israel Medical Center, New York, NY

Factors associated with HIV education attendance
R. Sterling(1), S. P. Weinstein(1), D. A. Calsyn(2), S. R. Doyle(2) and P. Crits-Cristoph(3), (1) Thomas Jefferson University, Philadelphia, PA, (2) University of Washington, Seattle, WA and (3) University of Pennsylvania, Philadelphia, PA

Racial disparities in quality of life of substance abusers in treatment
N. G. Forge(1), M. Y. Iguchi(1,2), E. Wong(4) and R. Bluthenthal(1,4), (1) RAND Corporation, Santa Monica, (2) School of Public Health and (3) Integrated Substance Abuse Research Program, University of California, Los Angeles, and (4) Charles R. Drew University School of Medicine and Science, Los Angeles, CA

Racial differences in syringe purchasing and carrying
W. Zule(1), E. Costenbader(1), K. S. Riehman(1), C. Coomes(1) and G. Bobashev(2), (1) Behavioral Health Research Divsion, and (2) Statistics and Epidemiology, RTI International, Research Triangle Park, NC

Symposium I - METHOD TO THE MADNESS: METHODOLOGY AND ANALYSIS OF CLINICAL TRIALS OF STIMULANT ABUSE PHARMACOTHERAPY

Chairs: John Grabowski and Marc Mooney

Medication evaluation in the laboratory: Predicting success or failure
Sharon Walsh, University of Kentucky, Lexington, KY

Quantification of stimulant use: Issues in identifying drug-use events
Kenzie Preston, Johns Hopkins Bayview Medical Center, Baltimore, MD

Defining substance-abuse treatment success: A comparison of major methods
Marc Mooney, University of Minnesota, Minneapolis, MN

Analyzing data from stimulant trials: State of the science
Kevin Delucchi, University of California, San Francisco, CA

Future directions for stimulant-abuse pharmacotherapy trials
Discussant: Mehmet Sofuoglu, Yale University, West Haven, CT

Oral Communications 1- WE HAVE CHEMISTRY

Chairs: Howard Deutsch and Mark Froimowitz

Slow onset, long duration methylphenidate analogs with selectivity for the dopamine transporter

M. Froimowitz(1), Y. Gu(1), L. A. Dakin(1), C. J. Kelley(1), D. Parrish(2), J. R. Deschamps (2), A. C. Pak(3), J. G. Gilbert(3), X. Q. Peng(3), Z. X. Xi(3) and E. L. Gardner(3), (1) Massachusetts College of Pharmacy, Boston, MA, (2) Naval Research Laboratory, Washington, DC and (3) NIDA Intramural Research Program, Baltimore, MD

Pharmacophore for methylphenidate at the dopamine transporter

H. Deutsch(1), M. M. Schweri(2) and D. I. Kim(1), (1) School of Chemistry, Georgia Tech, Atlanta, GA and (2) School of Medicine, Mercer University, Macon, GA

Novel dopamine D3 receptor ligands with functionalized linking chains as potential cocaine abuse therapeutic agents

P. Grundt(1), J. Cao(1), E. McElveen(2), R. R. Luedtke(2) and A. H. Newman(1), (1) Medicinal Chemistry Section, NIH/NIDA Intramural Research Program, Baltimore, MD and (2) University of North Texas Health Science Center, Fort Worth, TX

Pharmacokinetics of oral NRP104/SPD489 (lisdexamfetamine dimesylate) versus d-amphetamine in healthy adults with a history of stimulant abuse

S. Krishnan(1) and D. Jasinski(2), (1) New River Pharmaceuticals, Blacksburg, VA and (2) The Johns Hopkins University, Baltimore, MD

2-Fluoro-3-(4-nitro-phenyl)deschloroepibatidine, a novel competitive antagonist of human neuronal 4 2 nAChR, with possible utilization in treatment of nicotine dependence

G. Abdrakhmanova(1), M.I. Damaj(1), F.I. Carroll(2) and B.R. Martin(1), (1) Virginia Commonwealth University, Richmond, VA and (2) Research Triangle Institute, Research Triangle Park, NC

Synergistic design of polar bis-pyridinium analogs containing a 1,4-di-(1-butynyl)phenylenediyl linker: Interaction with both nicotinic receptors and the blood-brain barrier choline transporter

Z. Zhang(1), A. G. Deaciuc(1), P. R. Lockman(2), D. D. Allen(2), L. P. Dwoskin(1) and P. A. Crooks(1), (1) College of Pharmacy, University of Kentucky, Lexington, KY, and (2) School of Pharmacy, Texas Tech University, Amarillo, TX

An 8-[N-(4'-phenyl)-phenethyl carboxamido] analogue of cyclazocine

M. Wentland(1), M. VanAlstine(1), R. Kucejko(1), R. Lou(1), D. J. Cohen(2), A. L. Parkhill(2) and J.M. Bidlack(2), (1) Rensselaer Polytechnic Institute, Troy, NY and (2) University of Rochester, Rochester, NY

Ex-vivo study of long-lasting activity of the kappa-antagonist JDTic

I. Berzetei-Gurske(1), L. Jimenez(1), D. Haggart(1), F. I. Carroll(2) and L. Toll(1), (1) SRI International, Menlo Park, CA and (2) Research Triangle Institute, Durham, NC

Oral Communications 2 - GENES AND PROTEINS

Chairs: Rumi K. Price and Thomas A. Green

Proteomics-based analysis of cocaine addiction

N. Tannu(1), S. E. Hemby(1), L. Howell(2) and D. C. Mash(3), (1) Wake Forest University, Winston-Salem, NC, (2) Yerkes Primate Center, Emory University, Atlanta, Georgia, GA and (3) University of Miami, Miami, FL

Dopaminergic drugs regulate the expression of "clock" genes in striatal neurons

M. Imbesi, A. D. Arslan, H. Manev and T. Uz, Psychiatric Institute, Chicago, IL

Effect of environmental enrichment on transcription factors in the nucleus accumbens under basal conditions and after acute or repeated cocaine administration

T. A. Green(1), D. E. Theobald(1), M. T. Bardo(2) and E. J. Nestler(1), (1) UTSW, Dallas, TX and (2) University of Kentucky, Lexington, KY

Acute amphetamine induces nuclear PI3-kinase activity and rapid translocation of SGK1 and Akt1 to the nuclei of cells in rat striatum

J. F. McGinty, X. Shi and S. Toda, Medical University of South Carolina, Charleston, SC

COMT val(158)-met polymorphism may influence measures of impulsive behavior and drug use in heroin-dependent individuals: A preliminary analysis

M. K. Greenwald(1), L. Cederlind(1), E. Sliwerska(2) and M. Burmeister(2), (1) Wayne State University, Detroit, and (2) University of Michigan, Ann Arbor, MI

DRD2 Taq 1A allele is associated with pain response in Chinese male heroin-dependent subjects

M. C. Ho(1), K. L. Cheung(3), N. Tang(1), Y. K. Leung(1) and A. Stadlin(1,2), (1) Chinese University of Hong Kong, Shatin, Hong Kong, (2) School of Medical Science, Griffith University, Southport, Queensland, and (3) Substance Abuse Assessment Clinic, Kwai Chung Hospital, Tsuen Wan, Hong Kong

Dopamine transporter coding variant Ala559Val associated with attention deficit hyperactivity disorder causes of dopamine efflux

E. Bowton, M.S. Mazei-Robison, R.D. Blakely and A. Galli, Vanderbilt Univeristy, Nashville, TN

Modeling pleiotropy for family study data: Substance consumption comorbidity using GEE-2 linkage/association joint analysis

R. K. Price(1), N. K. Risk(1), J. Wang(1), J. Sakai(2) and J. Corbett(1), (1) Washington University School of Medicine, St. Louis, MO and (2) University of Colorado School of Medicine, Denver, CO

Oral Communications 3 - BRAIN DIFFERENCES IN HUMAN ADDICTION: CHICKEN AND/OR EGG?

Chairs: Thomas R. Kosten and Murat Yucel

Reduced visual and auditory brain activation in cocaine abusers

T. R. Kosten(1), K. A. Tucker(1), M. N. Potenza(2) and B. Wexler(2), (1) Yale University School of Medicine, VA Connecticut Healthcare System, West Haven, and (2) Yale University School of Medicine, Connecticut Mental Health Center, New Haven, CT

Dopamine D1 receptors in the ventral striatum measured with PET predict the choice to selfadminister cocaine

D. Martinez, R. W. Foltin, M. Slifstein, A. I. Broft, D. R. Hwang, A. Perez, R. Narendran and H. D. Kleber, Columbia University/New York State Psychiatric Institute, New York, NY

Cholinergic receptor systems in cocaine-addicted subjects: Alterations in regional cerebral blood flow

B. Adinoff(1), M.J. Williams(2), S.E. Best(1), T. Zieklinski(2), T.S. Harris(3) and M.D. Devous(3), (1) University of Texas Southwestern Medical Center and VA North Texas Health Care System, and (2,3) UT Southwestern Medical Center, Dallas, TX

The effects of protracted cocaine abstinence on depression, cognitive planning and brain metabolism

C. A. Hanlon(1), V. D. Weisser(1), L. B. Livengood(1), M. D. Miller(1), D. L. Flowers(2) and L. J. Porrino(1), (1) Department of Physiology and Pharmacology and (2) Department of Neurology, Wake Forest University, Winston-Salem, NC

Low resting perfusion in the anterior cingulate predicts increased depressive symptoms in cocaine-dependent patients

J. J. Suh(1), R. Ehrman(1,2), Z. Wang(1), Y. Li(1), J. G. Hakun(1), M. Goldman(1), R. Bernstiel(1), T. Franklin(1), C. P. O'Brien(1,2), J. Detre(1) and A. R. Childress(1,2), (1) Addiction Treatment Research Center, University of Pennsylvania, Philadelphia, PA and (2) Behavioral Health, VAMC, Philadelphia, PA

Altered affective responsivity in chronic marijuana smokers: An fMRI study

S. A. Gruber(1,2), J. Rogowska(1,2), J. Sneider(1,2) and D. Yurgelun-Todd(1,2), (1) Cognitive Neuroimaging Laboratory, McLean Hospital, Belmont, and (2) Harvard Medical School, Boston, MA

SPECT imaging of beta2 nicotinic acetylcholine receptors in tobacco smokers during acute and prolonged withdrawal

K. P. Cosgrove(1,2), E. B. Frohlich(1,2), E. Krantzler(1,2), S. S. Krishnan-Sarin(1), S. O'Malley(1), F. Bois(1,2), G. D. Tamagnan(3), J. P. Seibyl(3) and J. K. Staley(1,2), (1) Yale University School of Medicine, New Haven, (2) VA Connecticut Health Care System, West Haven, and (3) Institute for Neurodegenerative Disorders, New Haven, CT

Abnormal activation and reduced neuronal integrity of brain circuits involved in cognitive control in opiate users

M. Yucel(1,2,3), D. I. Lubman(1,3), K. Roffell(1), B. J. Harrison(2,3), T. MacKenzie(1), A. Fornito(2,3), N. B. Allen(1,3), S. J. Wood(2,3), R. Cunnington(3) and C. Pantelis(2,3), (1) ORYGEN Research Centre, (2) Melbourne Neuropsychiatry Centre, and (3) The University of Melbourne, Melboune, Victoria, Australia

Symposium II - DEVELOPMENTS IN METHAMPHETAMINE ABUSE TARGETS AND PHARMACOTHERAPIES

Chairs: Linda P. Dwoskin and Nathan M. Appel

Lobeline: A candidate pharmacotherapy for methamphetamine abuse

Linda P. Dwoskin, University of Kentucky, Lexington, KY

Treating methamphetamine addiction with vigabatrin

Stephen L. Dewey, Brookhaven National Laboratory, Upton, NY

Monoclonal antibody antagonists for treatment of medical problems associated with methamphetamine abuse

S. Michael Owens, University of Arkansas for Medical Sciences, Little Rock, AR

Angiotensin converting enzyme as a target for the treatment of methamphetamine dependence: Perinodopril methamphetamine interaction study

Thomas F. Newton, UCLA Geffen School of Medicine, Los Angeles, CA

Discussant

Nathan M. Appel, NIDA/DPMCDA, Bethesda, MD

Oral Communications 4 - IN SEARCH OF RELIEF: CHRONIC PAIN

Chairs: Leslie Amass and Deborah L. Haller

Epidemiological evidence for a link between pain and opioid abuse

R. A. Denisco, W. Compton, K. Conway, Y. Thomas and M. Brodsky, Division Epidemiology, Services and Prevention, NIDA/NIH, Bethesda, MD

Risk factors associated with abuse of prescription opioids: Results of a national survey

J. Tetrault, R. Desai, W. Becker, D. Fiellin, J. Concato and L. Sullivan, Yale University, New Haven, CT

Pain as a reason for seeking admission to methadone treatment

J. D. Haddox(1), M. Y. Smith(1), S. Colucci(1), A. Rosenblum(2), C. Fong(2), C. Maxwell(2) and M. Parrino(3), (1) Risk Management & Health Policy, Purdue Pharma LP, Stamford, CT, (2) National Development and Research Institutes, and (3) AATOD, New York, NY

Efficacy of dextromethorphan on opioid-induced hyperalgesia in methadone patients

P. Compton(1), W. Ling(2) and M. Torrington(2), (1) School of Nursing, UCLA, and (2) Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Counselor experiences working with methadone-maintained chronic pain patients: An exploratory study

D.T. Barry(1), M.J. Bernard(2), M. Beitel(1), B.A. Moore(1) and R.S. Schottenfeld(1), (1) Yale University, and (2) The APT Foundation, Inc., New Haven, CT

Does personality influence outcomes for Rx opioid abusers with pain?

D. L. Haller and M. C. Acosta, St. Luke's-Roosevelt Hospital Center, and Columbia University, New York, NY

Buprenorphine treatment as an alternative to orthopedic surgery in opioid-tolerant patients taking prescription opiates for severe pain

R. Chavez(1), W. Dillin(2) and L. Amass(3), (1) The P.A.I.N. Institute, Inc., Redondo Beach, (2) Kerlan-Jobe, and (3) Friends Research Institute, Inc., Los Angeles, CA

Psychiatric and substance abuse comorbidity influences treatment outcomes in opioid-abusing pain patients

M. Acosta and D.L. Haller, St. Luke's-Roosevelt Hospital and Columbia University, New York, NY

Oral Communications 5 - SMOKING: BENCH TO BEDSIDE

Chairs: Ian Stolerman and Susan Robinson

The role of nicotinic alpha7 receptors in the dopamine-mediated component of nicotine discrimination

I. Stolerman, D. Quarta, C. Naylor and C. Fernandes, Institute of Psychiatry, King's College London, London, UK

Rats exhibiting acute behavioral tolerance to nicotine show evidence of nicotinic cholinergic receptor (nAChR) desensitization

S. E. Robinson(1), J. R. James(2), R. E. Vann(1), A. F. Britton(1), M. M. O'Connell(1) and J. A. Rosecrans(1), (1) Department of Pharmacology & Toxicology, and (2) Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA

Rapid behavioral sensitization to amphetamine- and nicotine-stimulated locomotor activity in female rats

E. M. Jutkiewicz and M. E. Gnegy, University of Michigan, Ann Arbor, MI

MD-354 selectively attenuates the action of nicotine in the mouse tail-flick assay

M. Dukat, A. Wesolowska, S. Young, T. Bondareva, R. Young and R. A. Glennon, Virginia Commonwealth University, Richmond, VA

Effect of methylphenidate pretreatment on intravenous nicotine self-administration in rats

T. Wooters, N. M. Neugebauer and M. T. Bardo, University of Kentucky, Lexington, KY

Impulsivity and treatments for smoking: A laboratory model

B. R. Raiff and J. Dallery, University of Florida, Gainesville, FL

Comparison of the effects of binge smoking of low- and high-nicotine cigarettes on hypothalamic-pituitary-adrenal axis hormones and mood in men

J. H. Mendelson, N. V. Goletiani, M. B. Sholar, A. J. Siegel, R. A. Sewell and N. K. Mello, Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA

Smoking outcome expectancies predict nicotine withdrawal symptoms in mildly and moderately depressed college women smokers

A. Copeland(1) and G. S. Hecht(2), (1) Louisiana State University, and (2) Southern University, Baton Rouge, LA

Oral Communications 6 - PRECLINICAL STUDIES OF EARLY DRUG EXPOSURE
Chairs: Katherine L. Nicholson and Laura E. O'Dell

Enhanced cocaine-induced increases in dopamine and glutamate within the nucleus accumbens of prenatally stressed rats
T. E. Kippin, Z. Kapasova and K. K. Szumlinski, University of California at Santa Barbara, Santa Barbara, CA

Prenatal opiate exposure followed by postnatal withdrawal enhances the corticosterone response to cocaine in adult rats
L. Schrott and L. M. Franklin, LSU Health Sciences Center, Shreveport, LA

Prenatal exposure to toluene alters attention and impulsive behavior in rats in a "Waiting-for- Reward" task
P. Cooper(1), D. Williams(1), J. Batis(1), J. Hannigan(1,2) and S. Bowen(1,2), (1) Department of Psychology, and (2) Department of Obstetrics & Gynecology, Wayne State University, Detroit, MI

Prenatal exposure to toluene induces long-term behavioral deficits in mice when tested in animal models of anxiety
C. Lopez-Rubalcava, D. P. Ponce and S. L. Cruz, Farmacobiologia, Cinvestav-Sede Sur,

Comparison of conditioned place preference produced by ketamine in adolescent versus adult rats
K. L. Nicholson, R. L. Evans and R. L. Balster, Virginia Commonwealth University, Richmond, VA

The affective properties of nicotine withdrawal are diminished in adolescent versus adult rats
L. E. O'Dell, L. A. Natividad, O. V. Torres and H. A. Tejeda, University of Texas El Paso, El Paso, TX

Toward a functional understanding of adolescent dopamine function: Implications for addiction
Q. D. Walker, M. L. Johnson, J. C. Caster, N. L. Schramm-Sapyta and C. M. Kuhn, Duke Medical Center, Durham, NC

S-(+)-gamma vinyl-GABA (S-GVG) blocks the response to methamphetamine (METH) in adolescent and adult animals treated with METH and S-GVG during adolescence
S. L. Dewey(1,2), W. K. Schiffer(1), D. Lee(1), S. Aquilina(1), S. Kothari(1), U. Mullapudi(1), V. Patel(1), J. (1), E. Gardner(4), C. R. Ashby(3) and J. D. Brodie(2), (1) BNL, Upton, (2) NYU, New York, and (3) St. Johns University, Queens, NY; and (4) NIH, Baltimore, MD

Training Grant Mixer

Workshop I - NIDA WORKSHOP ON INTERNATIONAL RESEARCH AND COLLABORATION
Chair: Steven Gust

Workshop II - MATHEMATICAL MODELING IN BIOLOGICAL AND EPIDEMIOLOGICAL STUDIES OF DRUG ADDICTION
Chairs: Georgiy Bobashev and Boris Gutkin

Workshop III - WHAT'S NEW AT NIDA AND NIH: ELECTRONIC SUBMISSION OF APPLICATIONS AND MORE
Chairs: Mark R. Green, Teri Levitin, and Mark Swieter

Workshop IV - 12TH ANNUAL CONTINGENCY MANAGEMENT WORKING GROUP
Chair: Stacey Sigmon

Workshop V - HIV/AIDS RESEARCH IN THE NIDA CLINICAL TRIALS NETWORK: EMERGING RESULTS
Chair: James L. Sorensen

Monday, June 19, 2006

NIDA Forum I - THE NIH ROADMAP AND NEUROSCIENCE BLUEPRINT
Chair: Timothy P. Condon

Introduction - NIH-wide research initiatives
Timothy P. Condon, NIDA, Bethesda, MD

The NIH roadmap and neuroscience blueprint
Nora D. Volkow, NIDA, Bethesda, MD

The molecular library roadmap initiative: An overview
Glen Hanson, University of Utah Health Sciences Center, Salt Lake City, UT

Capitalizing on high throughput screening
David Weaver, HTS Center, Vanderbilt University, Nashville, TN

Chem-informatics and PubChem
Tudor Oprea, University of New Mexico School of Medicine, NM
Overview of the NIH neuroscience blueprint microarray facility
Dietrich Stephan, Translational Genomics Research Institute, Phoenix, AZ

Marian W. Fischman Memorial Award Lecture
Presentation of the Marian W. Fischman Memorial Award
Introduction by Stephen G. Holtzman
Marian W. Fischman Memorial Award Lecture
Linda Dykstra

POSTER SESSION II - PHARMACOKINETICS AND CHEMISTRY
Assessment of the pharmacokinetic and pharmacodynamic interaction of oral naltrexone when co-administered with oral hydrocodone/APAP
R. F. Kaiko, R. D. Colucci, C. D. Breder and C. Grudzinskas, Purdue Pharma L.P., Stamford, CT
Within-session operant responding is not determined by titration of nucleus accumbens dopamine or remifentanil, whole brain remifentanil, or blood remifentanil
G. Zernig(1), J. A. Crespo(1), C. W. Schindler(2), L. V. Panlilio(2), K. Sturm(1) and A. Saria(1), (1) Medical University, Innsbruck, Austria and (2) NIDA/NIH Intramural Program, DHHS, Baltimore, MD
Mechanisms underlying tramadol- and its active metabolite M1-induced pharmacological effects in mice
T. Suzuki, A. Nakamura, M. Suzuki, N. Kuzumaki and M. Narita, Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Tokyo, Japan
Toxicological analysis in rats subjected to heroin and morphine overdose
J. J. Strandberg(1), F. C. Kugelberg(1), K. Alkass(1), A. Gustavsson(1), K. Zahlsen(2,3), O. Spigset(2,3) and H. Druid(1), (1) Karolinska Institutet, Stockholm, Sweden, (2) St. Olav University Hospital, Trondheim, and (3) Children's and Women's Disease, Norwegian University of Science and Technology, Trondheim, Norway
The effect of opiates on the activity of human placental aromatase
O. Zharikova(1), S. Deshmukh(2), T. Nanovskaya(1), M. Kumar(1), R. Vargas(1), G. Hankins(1) and M. Ahmed(1), (1) OB/'GYN Maternal Fetal Medicine, University of Texas Medical Branch, Galveston, TX and (2) Merck and Company, Boston, MA
Transfer of methadone across preterm placentas and the role of the efflux transporter Pglycoprotein
T. Nanovskaya, I. Nekhayeva, O. Zharikova, G. Hankins and M. Ahmed, University of Texas Medical Branch, Galveston, TX
Buprenorphine metabolism by preterm human placentas
R. McRee(1), S. Ravindran(2), O. Zharikova(2), R. Vargas(2), T. Nanovskaya(2), G. Hankins(2) and M. Ahmed(2), (1) Department of Pharmacology and Toxicology, and (2) Department of OB/GYN Maternal Fetal Medicine, University of Texas Medical Branch, Galveston, TX
Electronic buccal drug delivery system to treat addiction and chronic diseases: A porcine study in the frame of "IntelliDrug" project
H. J. Mell(1), A. Wolf(2), B. Beyski(2) and M. Arieli(3), (1) Israel National AntiDrug Authority, Jerusalem, (2) Assuta Hospital, Tel Aviv, and (3) Health Ministery, Jerusalem, Israel
Structure-activity studies on JDTic: Functional analysis and antidiuretic activity
S. P. Runyon, H. Navarro, L. Brieaddy, J. Howard and F. I. Carroll, Organic and Medicinal Chemistry, Research Triangle Instutute, Research Triangle Park, NC
The relative activity of opioids as P-glycoprotein substrates
S. L. Mercer, C. W. Cunningham, H. Hassan, N. D. Eddington and A. Coop, University of Maryland, School of Pharmacy, Baltimore, MD
Bivalent ligands as probes for cannabinoid receptor oligomerization
Y. Zhang, B. F. Thomas, H. H. Seltzman and A. F. Gilliam, Research Triangle Institute, Research Triangle Park, NC
Pharmacokinetic factors associated with MDMA-induced 5-HT depletion in rats
D. Zolkowska(1), J. P. Pablo(2), R. B. Rothman(1) D.C. Mash(2) and M. H. Baumann(1), (1) NIH/NIDA, Intramural Research Program, Baltimore, MD and (2) University of Miami School of Medicine, Miami, FL
Self-administration as an assay system to measure the pharmacokinetic and pharmacodynamic potencies of receptor antagonists
W. R. Buesing, M. K. Norman, V. L. Tsibulsky and A. B. Norman, University of Cincinnati, Cincinnati, OH

Dopamine receptor antagonists accelerate cocaine self-administration by raising the satiety threshold

M. K. Norman, W. R. Buesing, M. R. Tabet, A. J. Pesce, V. L. Tsibulsky and A. B. Norman, University of Cincinnati, Cincinnati, OH

The safety and tolerability of 7.5, 15 and 30 mg of sublingual lobeline

R. T. Jones(2), E. Fernandez(2), A. Manari(2) and J. Mendelson(1,2), (1) Addiction Pharmacology Research, California Pacific Medical Center, and (2) Drug Dependence Research, UCSF, San Francisco, CA

A comparison of 8-hetero tropanes: Inhibition of monoamine uptake systems

P. C. Meltzer(1), B. K. Madras(2) and P. Duy-Phong(1), (1) Organix Inc., Woburn, MA and (2) New England Regional Primate Research Center, Southborough, MA

Synthesis of 4-{2-[bis(4-fluorophenyl)methoxy]ethyl}-1-(2-trifluoromethylbenzyl)piperidine, an allosteric modulator of the serotonin transporter

T.L. Boos, E. Greiner, W.J. Calhoun, T.E. Prisinzano, B. Nightingale, C.M. Dersch, R.B. Rothman, A.E. Jacobson and K.C. Rice, National Institute of Diabetes and Digestive and Kidney Diseases, DHHS, Bethesda, MD and National Institute on Drug Abuse, Addiction Research Center, NIH/NIDA, DHHS, Baltimore, MD

Attenuating the effects of cocaine with novel sigma receptor antagonists

T. A. Smith(1), B. Pouw(2), R. R. Matsumoto(2), J. Shaikh(2), J. Diers(2), J. Yu(2) and A. Coop(1), (1) University of Maryland School of Pharmacy, Baltimore, MD and (2) University of Mississippi School of Pharmacy, University, MS

Pharmacological and toxicological screening of a chimeric human anti-cocaine monoclonal antibody

M. R. Tabet(1), W. J. Ball(1), L. M. Friedman(1) and A. B. Norman(1,2), (1) University of Cincinnati, and (2) Phase 2 Discovery, Inc., Cincinnati, OH

A chimeric human anti-cocaine monoclonal antibody alters the distribution but not the metabolism of cocaine in mice

A. B. Norman(1,2), M. R. Tabet(1), M. K. Norman(2), W. R. Buesing(2), A. J. Pesce(1) and W. J. Ball(1), (1) University of Cincinnati, and (2) Phase 2 Discovery, Inc., Cincinnati, OH

Nicotine-specific monoclonal antibody (Nic311) pharmacokinetics in rats

S. A. Roiko(1,3), D. E. Keyler(2,3), M. G. LeSage(3) and P. R. Pentel(1,3), (1) University of Minnesota, (2) College of Pharmacy, University of Minnesota, and (3) Minneapolis Medical Research Foundation, Minneapolis, MN

Vaccination against nicotine does not prevent nicotine-induced changes in fetal nicotinic receptor binding and c-fos mRNA expression

P. P. Pentel(1,3), D. Keyler(1,3), Y. Chen(2), M. G. LeSage(1,3), M. B. Dufek(1) and F. M. Leslie(2), (1) Minneapolis Medical Research Foundation, Minneapolis, MN,
(2) University of California, Irvine, CA and (3) University of Minnesota, Minneapolis, MN

Novel trivalent antagonists with selectivity for alpha7 nicotinic acetylcholine receptors

R. L. Papke(1), G. Zheng(2), C. J. Burkle(1), P. A. Crooks(2) and L. P. Dwoskin(2), (1) Pharmacology and Therapeutics, University of Florida, Gainesville, FL and (2) Pharmaceutical Sciences, University of Kentucky, Lexington, KY

New leads for the treatment of nicotine addiction: Discovery of novel bis-quaternary ammonium antagonists at neuronal nicotinic receptors mediating nicotine-evoked dopamine release

G. Zheng, S. P. Sumithran, A. G. Deaciuc, L. P. Dwoskin and P. A. Crooks, University of Kentucky, Lexington, KY

New leads for the treatment of nicotine addiction: Discovery of novel tris-quaternary ammonium antagonists at neuronal nicotinic receptors mediating nicotine-evoked dopamine release

S. P. Sumithran, G. Zheng, A. G. Deaciuc, P. A. Crooks and L. P. Dwoskin, University of Kentucky, Lexington, KY

IMAGING

Age-dependent decreases in brain glutamate and GABA after acute toluene in juvenile and adolescent rats by high-resolution MRS

S. O'Leary-Moore(1,2), A. McMechan(2), M. Galloway(3), J. Hannigan(1,2) and S. Bowen (1,2), (1) Department of Psychology, (2) Department of Obstetrics & Gynecology, and (3) Department of Psychiatry & Behavioral Neuroscience, Wayne State University, Detroit, MI

Imaging changes in brain function and structure in an animal model of inhalant abuse

W. K. Schiffer(1), D. Lee(1), J. Carrion(1), E. L. Gardner(2) and S. L. Dewey(1), (1) Brookhaven National Laboratory, Upton, NY and (2) NIDA, Bethesda, MD

Chronic marijuana users show decreased integrity in neural pathways associated with executive function and memory

M. J. Wesley(1), C. A. Hanlon(1), L. B. Livengood(1), R. Kraft(2), J. Zhu(3), C. Wyatt(4) and L. J. Porrino(1), (1) Department of Physiology and Pharmacology, (2) Department of Biomedical Engineering, (3) Department of Radiology and Radiation Oncology, Wake Forest University School of Medicine, Winston Salem, NC and (4) Virginia Tech, Blacksburg, VA

Brain imaging study of orientation and motor coordination in regular users of marijuana

A. M. Weinstein(1,2), O. Brickner(2), H. Lerman(2), M. Greemland(2), M. Bloch(5), R. Mechoulam(3), H. Lester(1), R. Bar-Hamburger(4), R. Chisin(1) and E. Even-Sapir(2), (1,3) Hadassah Hospital, and (4) Israeli Anti-drug Authority, Jerusalem, (2,5) Sourasky Medical Center, Tel Aviv, Israel

Changes in regional blood volume during a 28-day period of abstinence in chronic cannabis smokers

J. T. Sneider(1,3), H. G. Pope(2,3), M. M. Silveri(1,3), S. A. Gruber(1,3), J. Rogowska(1,3) and D. A. Yurgelun-Todd(1,3), (1) Department of Cognitive Neuroimaging, and (2) Department of Biological Psychiatry, McLean Hospital, Belmont, MA, and (3) Harvard Medical School, Boston, MA

An MR-compatible device for delivering smoked marihuana or tobacco to participants during functional imaging

B. Frederick(1,3), K. P. Lindsey(2,3), L. D. Nickerson(1,3) and S. E. Lukas(2,3), (1) Brain Imaging Center, and (2) Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA and (3) Harvard University Medical School, Boston, MA

BOLD fMRI of tobacco smoking

K. P. Lindsey(1), B. B. Frederick(2), L. D. Nickerson(1,2) and S. E. Lukas(1), (1) Behavioral Psychopharm Research Laboratory and (2) Brain Imaging Center, McLean Hospital, Belmont, MA

Neural activation during smoking self-control: fMRI assay

E. D. London(1,3), J. Monterosso(1), T. Mann(2), A. Ward(4), G. Ainslie(5), J. Xu(1), A. Brody(1), S. Engel(2) and M. Cohen(1), (1,2,3,4) Swarthmore College, Swarthmore, and (5) Coatesville VA Medical Center, Coatesville, PA

Neural correlates of nicotine withdrawal- versus cue-based craving

K. Drexler(1,2), A. Alford(1), K. Harenski(1) and C. Kilts(1), (1) Emory University, Atlanta, and (2) Atlanta VAMC, Decatur, GA

Smoking cue-induced brain activity shortly after quitting

M. Daamen(1), K. Specht(2,3), J. Reul(3,4), J. Ruhlmann(3) and C. G. Schutz(1), (1) Friedrich-Wilhelm-University Bonn, Bonn, Germany, (2) University of Bergen, Bergen, Norway, (3) MCB, Bonn, Germany and (4) KKH, Siegen, Germany

Optimizing analyses of arterial spin labeling perfusion fMRI for drug abuse studies

Z. Wang(1,2), T. Franklin(2), Y. Li(2), C. P. O'Brien(2,3), J. A. Detre(1) and A. R. Childress(1,3), (1) Department of Neurology, and (2) Department of Psychiatry, University of Pennsylvania; and (3) VA Medical Center, Philadelphia, PA

Connectivity analyses reveal a limitation of fast event-related fMRI designs with arousing stimuli: "Carry-over" effects

Y. Li, Z. Wang, R. Ehrman, T. Franklin, D. Langleben, C. P. O'Brien and A. R. Childress, University of Pennsylvania School of Medicine, Philadelphia, PA

Activation of the hypothalamus characterizes the response to acupuncture stimulation in heroin addicts: A functional MR imaging study

S. Liu(1), W. Zhou(1), L. Li(1), Z. Yang(2), F. Zhang(1), X. Weng(2) and G. Yang(1), (1) Ningbo Addiction Research and Treatment Center, Ningbo, Zhe Jiang, China and (2) Institute of Psychology, Chinese Academy of Sciences, Beijing, China

Tetrahydropalmatine induces a negative BOLD signal in the nucleus accumbens and orbitofrontal cortex in heroin-dependent rats

S. Li(1), G. Xu(1), Q. Yin(1), G. Wu(1) and Z. Yang(2), (1) Medical College of Wisconsin, Milwaukee, WI and (2) Beijing Institute of Basic Medical Science, Beijing, China

Both error monitoring and delay discounting activity co-localize in medial frontal cortex

S. D. Forman(1,2), G. G. Dougherty(1,2), L. A. Pisarov(1), G. Haas(1,2) and L. Kugler(1), (1) Pittsburgh Veterans' Affairs Healthcare System, and (2) University of Pittsburgh, Pittsburgh, PA

Brain structure in substance-dependent patients with and without Antisocial Personality Disorder

M. Holloway(1), R. Pratiwadi(2), M. Rusten(1), S. Busch(1), J. Hakun(1), R. Ehrman(1), C. P. O'Brien(1), A. R. Childress(1) and D. D. Langleben(1), (1) Addiction Treatment Research Center and (2) Brain Behavior Laboratory, University of Pennsylvania, Philadelphia, PA

Cerebral metabolism in cocaine dependence with comorbid major depression

E. Rubin, P. J. McGrath, A. Bisaga, W. N. Raby, B. A. Fallon, H. A. Sackeim and E. V. Nunes, Columbia University/New York State Psychiatric Institute, New York City, NY

Imaging dopamine release in alcohol and cocaine abuse

D. F. Wong(1,2), W. Ye(1), Y. Zhou(1), H. Kuwabara(1), A. Kumar(1), J. Brasic(1), M. Alexander(1), A. Nandi(1), M. McCaul(2), C. Munro(3), D. Janinski(3) and G. Wand(3), (1)Department of Radiology, (2) Department of Psychiatry, and (3) Department of Medicine, Johns Hopkins University, Baltimore, MD

Reciprocal T2RT fluctuations in striatum and cerebellar vermis correlate with subjective desire following oral methylphenidate

C.M. Anderson, M.H. Teicher, M.M. Silveri, S.E. Lukas, P.F. Renshaw and M.J. Kaufman, Brain Imaging Center, McLean Hospital/Harvard Medical School, Belmont, MA

Yoga sessions increase brain GABA levels

C. Streeter(1,3,4,5), J. E. Jensen(3,4), R. M. Perlmutter(1), H. J. Cabral(2), H. Tian(1), S. C. Xi(1), D. B. Terhune(1), D. A. Ciraulo(1,3,5) and P. F. Renshaw(1,2,3), (1) Dept. of Psychiatry, and (2) Boston U. School of Med, (3) Harvard Med. School McLean Hospital, Belmont, MA, (4) Dept. of Biostatistics, and (5) Boston VA Healthcare System, Boston, MA

Temporal lobe volumetric assessments in prenatally cocaine-exposed adolescents: Correlation with performance on the Rey-Osterrieth Complex Figure

G. R. Simpson(1), V. Govindaraju(1), C. Leonard(2), V. Moodley(1), B. C. Bowen(1), C. E. Morrow(1), P. Mundy(1), A. Maudsley(1) and E. S. Bandstra(1), (1) University of Miami, Miami, FL and (2) University of Florida, Gainesville, FL

Despite prolonged abstinence functional activity in response to cocaine self-administration remains reduced in the temporal lobe of rhesus monkeys

T. J. Beveridge, H. R. Smith, M. A. Nader and L. J. Porrino, Wake Forest University Health Sciences, Winston Salem, NC

Absence of recovery of the cerebral metabolic response to cocaine in monkey striatum following prolonged abstinence from chronic self-administration

H. R. Smith, T. J. Beveridge, M. A. Nader and L. J. Porrino, Wake Forest University Health Sciences, Winston-Salem, NC

Low resting perfusion in the ventromedial prefrontal cortex and amygdala of cocaine-dependent patients predicts poor response inhibition in a novel Affect-Congruent Go NoGo task

M. Goldman(1), R. N. Ehrman(1,2), Z. Wang(1), Y. Li(1), J. G. Hakun(1), M. R. MacDougall(1), J. J. Suh(1), C. P. O'Brien(1,2), J. Detre(1) and A. R. Childress(1,2), (1) Addiction Treatment Research Center, University of Pennsylvania, and (2) Behavioral Health, VAMC, Philadelphia, PA

Imaging response inhibition in cocaine-dependent patients using a stop-signal task

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Cerebral metabolic differences between completers and dropouts in cocaine dependence treatment

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COCAINE, AMPHETAMINES: HUMAN STUDIES I

Dependent vs. non-dependent cocaine users: Cocaine pharmacodynamics, self-administration

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Does personality predict performance on behavioral tasks of inhibitory control in cocaine abusers?

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Psychiatric symptoms may influence the performance of cocaine-dependent subjects in a new neuropsychological battery sensitive to prefrontal functions

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Electrocardiographic changes during cocaine withdrawal

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Psychological manipulations of indices of cardiovascular and cerebrovascular blood flow velocity in cocaine abusers

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Daily stressor sensitivity, abuse effects, and cocaine use in cocaine dependence: Gender differences

A. E. Waldrop, S. E. Back, K. T. Brady, H. P. Upadhyaya, A. L. McRae and M. E. Saladin, CNS Division, Medical University of South Carolina, Charleston, SC

Relationship of prolactin response to meta-chlorophenylpiperazine with severity of drug use in cocaine dependence
K. P. Hill(1), P. Mannelli(2), K. Peindl(2), T. Lee (2), C Davidson(2), E. Ellinwood(2), C. Kuhn(2) and A. A. Patkar(2), (1) Yale University, New Haven, CT and (2) Duke University, Durham, NC

Association between platelet serotonin transporter availability, prolactin response to metachlorophenylpiperazine and treatment outcome in cocaine dependence
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Comparison of the endocrine effects of the mixed mu/kappa opioid nalbuphine in combination with cocaine and cocaine alone in men
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Acute effects of cocaine in two models of inhibitory control: Implications of non-linear dose effects
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Effect of cocaethylene on acute responses to cocaine
J. R. Baker(1), P. Jatlow(2) and E. McCance-Katz(1), (1) Virginia Commonwealth University, Richmond, VA and (2) Yale University, New Haven, CT

Learning and memory deficits in abstinent cocaine and alcohol abusers: Relationship to drug and alcohol craving
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Equivalence learning in cocaine-dependent individuals
C. E. Myers(2), N. P. Vadhan(1), E. Rubin(1), D. Shohamy(3), R. W. Foltin(1) and M. A. Gluck(2), (1) Columbia University & New York State Psychiatric Institute, New York, NY, (2) Rutgers University, Newark, NJ and (3) Stanford University, Stanford, CA

Effects of abstinence reinforcement on the frequency and enjoyability of pleasant activities during treatment for cocaine dependence
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Attentional bias towards cocaine-related stimuli: A comparison of cocaine-dependent treatment seekers and non-treatment seekers
N. P. Vadhan(1), K. M. Carpenter(1), M. L. Copersino(2), C. L. Hart(1), E. V. Nunes(1) and R. W. Foltin(1), (1) Columbia University and New York State Psychiatric Institute, New York, NY and (2) McLean Hospital, Harvard Medical School, Belmont, MA

Changes in cocaine craving, mood and stress in cocaine-dependent individuals during inpatient treatment and outpatient follow-up
K. L. Bergquist, P. Paliwal, S. M. Hyman and R. Sinha, Yale University School of Medicine, New Haven, CT

Cocaine vaccine: Smoked cocaine administration in humans
M. Haney(1,2), E. W. Gunderson(1,2), E. D. Collins(1) and R. W. Foltin(1,2), (1) Columbia University, and (2) New York State Psychiatric Institute, New York, NY

Factors involved in predicting the success of Modafinil for the treatment of cocaine-dependent subjects
A. N. Starosta, C. Rha, T. Whittingham, D. DiDonato, K. Lynch, K. Kampman and C. Dackis, University of Pennsylvania, Philadelphia, PA

Addiction severity in cocaine-treatment seekers: An application of finite mixture modeling
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Advantage of a drug-specific ASI drug composite index: Validity of an ASI cocaine index for cocaine dependence
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Predictors of treatment outcome among cocaine-dependent individuals
F. Garawi, A. Bisaga, E. Nunes, E. Aharonovich, W. Raby, E. Rubin and F. Levin, Division of Substance Abuse, Columbia University, New York, NY

A data analysis procedure to identify efficacious components in a multi-component intervention for homeless cocaine-dependent clients
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Reliability of diagnostic information and validation by toxicological testing in postmortem drug abuse cases
Z. R. Afanador(1), A. Deep-Soboslay(2), G. Gallegos(1), M. A. Huestis(3), R. H. Lowe(3), A. J. Barnes(2), T. M. Hyde(2), J. E. Kleinman(2), E. Lehrmann(1), W. J. Freed(1) and M. M. Herman(2), (1) Cellular Neurobi and (2) NIH/NIMH, Bethesda, (3) Chem. and Drug Metab., NIDA/NIH Intramural Research Program, Baltimore, MD

The rise of methamphetamine use among American Indians in Los Angeles County

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GENES AND PROTEINS

Genetic influences on the relative reinforcing value of nicotine

R. Ray(1), C. Lerman(2), C. Jepson(2), F. Patterson(2), A. Strasser(2), M. Rukstalis(2), K. Perkins(3), K. Lynch(2), S. O'Malley(4) and W. Berrettini(2), (1) Dept. of Pharmacology, and (2) Dept. of Psychiatry, U. of Pennsylvania, Philadelphia, (3) U. of Pittsburgh School of Medicine, Pittsburgh, PA and (4) Yale School of Medicine, New Haven, CT

Association analysis of the protein phosphatase regulatory subunit B1 gene with nicotine dependence in European-Americans and African-Americans

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Gene expression profiles in cortical neurons treated with nicotine, ethanol, or both using a pathway-focused cDNA microarray

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Potential role of 14-3-3 proteins in THC-mediated neuroprotection

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Genetic variability at brain-derived neurotrophic factor in opioid dependence

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The melatonin / melatonin receptor system in regulating both striatal "clock" gene expression and the development of cocaine-induced behaviors

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Homer1a is not necessary for behavioral responsiveness to cocaine

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Regional differences in the effects of withdrawal from repeated cocaine upon CC-Homer protein expression: A two-species comparison

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Gender differences in association of the hPer2 gene polymorphisms with cocaine dependence

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Contrasting genetic models for lifetime comorbidity of cannabis and OID use and problem use in Australian adult twins

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Genetic and environmental vulnerabilities underlying adolescent substance use and problem use: General or specific?

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Ethical issues in substance use disorder genetics: Researchers' perspectives

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OPIATES: MECHANISMS AND BEHAVIOR II

Effects of the delta opioid receptor agonist SNC80 on intracranial self-stimulation in rats

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Neural substrates of relapse to heroin-seeking using a reinstatement model in rats

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Changes in acoustic startle and fear-potentiated startle during withdrawal from chronic opiate exposure in rats

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Protracted withdrawal in morphine-dependent rhesus monkeys: Physiological and behavioral effects
G.L. Becker and C.P. France, University of Texas Health Science Center, San Antonio, TX
Dextrorphan tartrate produces tolerance and physical dependence in rhesus monkeys
M.D. Aceto, E.R. Bowman and L.S. Harris, Virginia Commonwealth University, Richmond, VA
Inhibitory effects of mecamylamine on serum corticosterone increase precipitated by naloxone in morphine-dependent mice
S. Kishioka, T. Maeda, W. Hamabe, Y. Fukazawa, K. Kumamoto, A. Yamamoto, L. Shang and C. Yamamoto, Wakayama Medical University, Wakayama, Japan
Behavioral effects of thienorphine in rhesus monkeys
J. X. Li, G. L. Becker and C. P. France, University of Texas Health Science Center at San Antonio, San Antonio, TX
Dynamic reinforcing environments and the anhedonic hypothesis
C.F. Aparicio, Center of Studies of Alcoholism and Addictions, University of Guadalajara,
Do natural rewards and drugs of abuse interact with midbrain dopamine?
F. J. Velasco and C. F. Aparicio, Center of Studies of Alcoholism and Addictions, University of Guadalajara, Guadalajara, Jalisco, Mexico
Dopamine agonists and antagonists in the dynamics of choice
J.A. Balderrama and C.F. Aparicio, Center of Studies of Alcoholism and Addictions, University of Guadalajara, Guadalajara, Jalisco, Mexico
Subjective and miotic effects of prescribed doses of oxycodone and hydrocodone in volunteers
J. P. Zacny and S. Gutierrez, University of Chicago, Chicago, IL
Factors associated with recreational opioid use in heroin-dependent research volunteers
C. L. Steinmiller and M. K. Greenwald, Wayne State University, Detroit, MI
Predictors of heroin seeking, purchasing and consumption
J. K. Roddy(1,2) and M. K. Greenwald(1), (1) SARD, Wayne State University, Detroit, and (2) University of Michigan, Deaborn, MI
Kratom use by online opioid analgesic abusers
E.W. Boyer and K. Babu, University of Massachusetts Medical School, Worcester, MA

OPIATES: TREATMENT II
Effects of depot naltrexone on response to IV heroin in humans
M. A. Sullivan, S. K. Vosburg and S. D. Comer, Columbia University/New York State Psychiatric Institute, New York, NY
Tissue compatability, biodegradability, blood levels and opioid overdose following treatment of heroin-dependent persons with sustained-release naltrexone-poly(dl-lactide) implants
G. K. Hulse, University of Western Australia, Nedlands, Western Australia, Australia
Late insomnia as a predictor of treatment retention in naltrexone maintenance for heroin dependence
S.J. Anen, M.A. Sullivan, S. Shakibaie, S.K. Vosburg and E.V. Nunes, New York State Psychiatric Institute, New York, NY
Patient commitment language strength predicts outcome in behavioral naltrexone therapy involving significant others
A. C. Brooks(1), P. Amrhein(3,2), K. M. Carpenter(1,2), L. Curtiss(1), S. Anen(1) and E. V. Nunes(1,2), (1) New York State Psychiatric Institute, and, (2) College of Physicians and Surgeons, Columbia University, New York, NY and (3) Montclair State University, Montclair, NJ
Moderate marijuana use extends retention in a clinical trial of behavioral naltrexone therapy for heroin dependence
W. N. Raby(1), K. M. Carpenter(1), J. L. Rothenberg(1), M. A. Sulllivan(1), S. H. Church(2), A. Seracini(1), H. D. Kleber(1) and E. V. Nunes(1), (1) Columbia University and New York State Psychiatric Institute, New York, and (2) Montefiore Medical Center, Bronx, NY
Stress and drug-cue-induced craving in opioid-dependent individuals on naltrexone
S. M. Hyman, H. Fox and R. Sinha, Yale University School of Medicine, New Haven, CT
Low-dose naloxone challenge for quantitative opioid dependence measurement
S. Stine, M. Greenwald, D. Tansil and C. Schuster, Wayne State University, Detroit, MI
Medication of L-tetrahydropalmatine significantly increased the abstinence rate in heroin addicts
Z. Yang(1), H. Chen(2), W. Hao(2), G. Jin(3) and S. Li(4), (1) Beijing Institute of Basic Medical Science, Beijing, (2) Mental Health Institute of Xiangya Medical School, Changsha, and (3) Shanghai Institute of Medicine, Shanghai, China; and (4) Medical College of Wisconsin, Milwaukee, WI
Cooperation and defections among opioid-dependent patients and college students
M. L. Miller(1), R. Yi(1), A. Buchhalter(2), R. Landes(1) and W. Bickel(1), (1) University of Arkansas for Medical Sciences, Little Rock, AR and (2) Pinney Associates, Bethesda, MD

The importance of early progress in treatment for female substance abusers
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Relationship between intimate partner violence and health status among drug-dependent women in drug treatment
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The role of community support in treatment entry and retention
S. M. Kelly(1), R. P. Schwartz(1), K. E. O'Grady(2), H. S. Reisinger(1,3), J. Peterson(1) and B. S. Brown(4), (1) Friends Research Institute, Baltimore, MD, (2) University of Maryland, College Park, MD, (3) Johns Hopkins School of Public Health, Baltimore, MD and (4) University of North Carolina, Wilmington, NC

Differences in characteristics between in- and out-of-treatment heroin addicts
R. P. Schwartz(1), S. M. Kelly(1), H. S. Reisinger(1), K. E. O'Grady(2) and B. S. Brown(1,3), (1) Friends Research Institute, Baltimore, MD (2) University of Maryland, College Park, MD and (3) University of North Carolina, Wilmington, NC

Sense of coherence as a stable predictor for methadone maintenance treatment outcome
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Premature discharge from opioid treatment programs: Patients' perspectives
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Mortality among opioid-dependent clients in a longitudinal study
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What are the 3-year outcomes of treatment for heroin dependence in Sydney, Australia? Findings from the Australian Treatment Outcome Study
M. Teesson(1), J. Ross(1), S. Darke(1), K. Mills(1), A. Williamson(1), A. Havard(1) and M. Lynskey(2), (1) National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia and (2) Washington University, St Louis, MO

Guilt, shame, and compromise of fathering: A comparative study of drug-abusing men
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PSYCHIATRIC COMORBIDITY II

Measuring substance use outcome in dually diagnosed patients: A comparison of three methods
R. D. Weiss, M. L. Griffin, W. B. Jaffee, F. Graff and R. E. Bender, McLean Hospital, Belmont, MA

Comparing service delivery strategies for treating psychiatric comorbidity in opioid-dependent patients receiving methadone: Preliminary associations with onset of care and adherence
R. Brooner, V. King, K. Neufeld, K. Stoller, J. Peirce, G. Gallucci and M. Clark, Johns Hopkins University, Baltimore, MD

Implementation of best practices for clients with co-occurring substance use disorders and mental illness
H. J. Gotham, R. Claus, A. Homer and K. Selig, Missouri Institute of Mental Health/ University of Missouri, St. Louis, MO

Dually diagnosed patients returning home after hospitalization: Exploring treatment continuity using data-mining techniques
G. Stahler(1), J. Mennis(1), S. Mazzella(1) and R. Spiga(2), (1) Temple University, and (2) Temple University School of Medicine, Philadelphia, PA

Examination of dually diagnosed patients' participation in a contingency management program
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Functional Analytic Structured Systemic Treatment: A treatment for co-occurring mental illness and substance use disorders
R. Spiga, D. Haas, A. Wells, G. Stahler, K. Riley, W. Dubin and D. Baron, Temple University, Philadelphia, PA

Malingering detection in psychiatric inpatients: An exploratory study
A. Wells(1), R. Spiga(1) and K. Riley(2), (1) Temple University School of Medicine, and (2) Temple University, Philadelphia, PA

Screening and brief intervention for mental health disorders within alcohol and other drug services: The PsyCheck Project
N. K. Lee(1), L. L. Jenner(2), A. Baker(3), A. Ritter(1), L. Hides(4), J. Norman(1), K. Hall(1), F. Kay-Lambkin(3) and F. Dann(1), (1) Turning Point Alcohol and Drug Centre, Fitzroy, Victoria, (2) JenCo Consulting, ,Queensland, (3) University of Newcastle, Newcastle, New South Wales, and (4) Orygen Youth Health, Parkville, Victoria, Australia

Impact of group motivational interviewing on stages of change in dually diagnosed inpatients

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The relationship between therapist adherence and patients' responses to motivational interviewing, and treatment adherence in co-occurring disorders

M. E. Lavery(1), M. V. Pantalon(1) and A. J. Swanson(2), (1) Yale University School of Medicine, New Haven, CT and (2) Albert Einstein College of Medicine, Bronx, NY

Effective use of motivational skills by therapists improves client mental health and substance use status

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Psychosocial benefits associated with participation in a self-help group for patients with comorbidity

A. Rosenblum(1), S. Magura(1), C. L. Villano(1), C. Fong(1), H. Vogel(1,3), T. Betzler(2) and A. Laudet(1), (1) National Development and Research Institutes, Inc., New York, (2) Albert Einstein College of Medicine, Bronx, and (3) Double Trouble in Recovery, Inc., Brooklyn, NY

Participation in self-help groups for dually diagnosed persons is associated with increased confidence to cope with mental illness

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Clinician referral and treatment practices to promote self-help attendance for clients with cooccurring disorders

R. Claus(1), A. Wendler(2), and H. J. Gotham(1), (1) Missouri Institute of Mental Health, St. Louis, and (2) Mid-America Addiction Technology Transfer Center, Kansas City, MO

A longitudinal investigation of intimate partner violence among mothers with co-occurring mental illness and substance abuse disorders

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Relationship between military service and substance abuse among homeless dually diagnosed veterans

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Substance abuse treatment among adults with severe mental illness

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Categorical versus dimensional analysis of substance use severity in individuals with co-occurring psychiatric and substance use disorders

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Prevalence of psychiatric disorders and relationship with severity of substance use disorders

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Psychiatric distress among adult recent-onset cannabis users

Y. G. Flores-Ortega, C. F. Rios-Bedoya and J. C. Anthony, Michigan State University, East Lansing, MI

Psychiatric disorders and dependence in cannabis users that seek treatment vs. a random police-selected group of users

C. Arkaitz, C. Petrissan, V. Beltran, C. Denis, E. Lavie, M. Fatseas, J. Daulouede and M. Auriacombe, Universite Victor Segalen Bordeaux 2, Bordeaux Cedex, and Centre d'addictologie, BIZIA, Bayonne, France

Hospital stays for drug-related psychotic episodes in Australia, 1993-2004

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Risk for involvement in violence in persons with single disorders (substance use or major mental disorders) and with co-occurring substance use and mental disorders

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Influences of substance abuse and mental illness on incidents of violence and victimization

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CRIMINAL JUSTICE

The relationship between mental illness or substance abuse treatment and criminal behavior

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Treatment dropout among inner-city residential treatment-seeking substance users as a function of the interaction between antisocial personality disorder and court-mandated treatment status

C. W. Lejuez, S. B. Daughters, M. N. Sargeant, M. A. Bornovalova and B. A. Kohrt, University of Maryland, College Park, MD

Predictors of return-to-prison following community treatment for substance-abusing female offenders

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Gender differences in treatment engagement among a sample of incarcerated substance abusers

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The complex issue of treatment readiness in an offender population

E. A. Sears(1), T. W. Kinlock(1,4), K. E. O'Grady(2), J. M. Callaman(1) and B. S. Brown(3), (1) Friends Social Research Center, Baltimore, (2) University of Maryland College Park, College Park, MD, (3) University of North Carolina at Wilmington, Wilmington, NC, and (4) University of Baltimore, Baltimore, MD

Twelve-month return-to-custody rates among prison-based therapeutic community program participants compared to a no-treatment matched comparison group

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Five years after: Long-term recovery from heroin use among ex-offenders

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Attachment and social support among women drug offenders in community treatment

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Deconstructing HIV prevention interventions among drug abusing female offenders: Preliminary results of long-term follow-up efforts

C. F. Vemulapalli, C. Callahan, A. Ben Abdallah and L. B. Cottler, Washington University School of Medicine, St. Louis, MO

Arrest history as a critical indicator of risk among cocaine-using women

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Rural stimulant use and criminality in three states

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Illicit drug use initiation in prison

G. Caraballo, C. E. Albizu and A. Hernandez, Center for Evaluation and Sociomedical Research, Graduate School Public Health, University of Puerto Rico, San Juan, Puerto Rico

Measuring crime around methadone clinics: Does type of crime data make a difference?

S. J. Boyd(1), K. Armstrong(2), L. Fang(1), D. Medoff(1), L. Dixon(1) and D. A. Gorelick(3), (1) University of Maryland School of Medicine, Baltimore, MD (2) University of Maryland Baltimore County, Catonsville, and (3) NIH/NIDA/Intramural Research Program, Baltimore, MD

Criminal justice as a purchaser of community treatment

S. Kubiak, C. Arfken, A. Koch and E. Agius, Wayne State, Detroit, MI

Treating drug-offenders: Outcomes of California's Proposition 36

J. Chun(1), J. Guydish(1), J. L. Sorensen(1), N. Haug(1) and M. Spencer(2), (1) University of California, San Francisco, and (2) Walden House, Inc., San Francisco, CA

POLICY

Results of state policy change to place clients in more appropriate treatment settings

S. Stevens-Manser(1), M. Arocena(2), D. Wanser(2) and R. T. Spence(1), (1) Center for Social Work Research, University of Texas at Austin, and (2) Department of State Health Services, Austin, TX

A comparison of homeless substance-abusing individuals entering the VA homeless service and state shelter systems

A. Kline and D. Smelson, University of Medicine and Dentistry of New Jersey, Piscataway, NJ

A study to develop a Native American curriculum for state-accredited, non-tribal substance abuse programs in South Dakota

D. Mackey(2), F. Zavdil(2), M. Baron(2) and A. H. Skinstad(1), (1) University of Iowa, College of Public Health, Iowa City, IA and (2) University of South Dakota, Vermillion, SD

Katrina and Rita—who got treated?

J. C. Maxwell(1) and D. Walsh(2), (1) Center for Social Work Research, University of Texas at Austin, and (2) Department of State Health Services, Austin, TX

The incremental inpatient health service costs associated with marijuana comorbidity

R. L. Pacula(1), J. Ringel(1), C. Dobkin(2) and K. Truong(1), (1) Drug Policy Research Center, RAND, Santa Monica, and (2) University of California Santa Cruz, Santa Cruz, CA

Interpersonal dynamics and treatment barriers: An ethnographic study of drug-using couples

J. Simmons, National Development and Research Institutes/MHRA, New York, NY

Disclosure of sensitive information in non-treatment-seeking post-partum women: A randomized trial of four approaches to participant protection

S. K. Chase and S. J. Ondersma, Wayne State University, Detroit, MI

The impact of parental substance abuse on the lives of domestic violence survivors

T. Jospitre(1), R. E. Sage(1,2), M. Chu(1,2), S. Griffing(1), L. Madry(1) and B. J. Primm(1,2), (1) Urban Resource Institute, Brooklyn, and (2) Addiction Research and Treatment Corporation, Brooklyn, NY

Behavioral contingencies can reduce the costs of counseling services in adaptive stepped-care treatment approaches

K. Stoller(1), P. Alexandre(2), E. Strain(1), M. Kidorf(1), V. King(1) and R. Brooner(1), (1) Johns Hopkins University School of Medicine, and (2) Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Perceived medical effectiveness and buprenorphine use

C.L. Arfken, S. Menza and C. R. Schuster, Wayne State University, Detroit, MI

LITERATURE REVIEW

Prescription opioid abuse: Review of current surveillance systems

N. Katz(1,3), H. Chilcoat(2), S. Butler(1), S. Budman(1), A. Villapiano(1), A. Licari(1), B. Houle(1), R. Colucci(4) and E. Adams(5), (1) Inflexxion, Inc., Newton, MA (2) Johns Hopkins Bloomberg Sch. of Public Health, Baltimore, MD (3) Tufts U. Sch. of Medicine, Boston, MA (4) Colucci & Assoc., LLC, Newtown, CT and (5) Covance Inc., Princeton, NJ

A systematic review of harm reduction

A. Ritter, Turning Point, Melbourne, Victoria, Australia

Clinical supervisors as translators and transmitters of evidence-based practices: A five-state survey of clinical supervisors working in substance abuse community treatment programs

M. C. Leone(1), N. A. Roget(1), J. Norland(1) and A. H. Skinstad(2), (1) University of Nevada, Reno, NV and (2) University of Iowa, Iowa City, IA

Substance abuse and older adults: A review of the literature

L. Hess(1), K. Munly(1), I. James(3), S. Nemes(3), L. Pelletier(1) and E. Moolchan(2), (1) Public Health Research, Danya International, Inc., Silver Spring, (2) HHS/NIH/ NIDA/IRP, Baltimore, and (3) Social Solutions International, Inc., Olney, MD

The changing face of the substance abuse treatment workforce: Is a crisis imminent? Implications for researchers, providers, and educators

S. A. Storti(2), N. A. Roget(1), E. A. Albers(1) and A. H. Skinstad(3), (1) University of Nevada, Reno, Reno, NV, (2) Brown University, Providence, RI and (3) University of Iowa, Iowa City, IA

Adherence and response to hepatitis C treatment among injection drug users

C. Heckman(1) and K. Cropsey(2), (1) Department of Psychiatry, and (2) Department of Criminal Justice, Virginia Commonwealth University, Richmond, VA

Opioid withdrawal scales: SOWS, OOWS and more SOWS

A. Elkader(1,2) and B. A. Sproule(1,2), (1) Centre for Addiction and Mental Health, and (2) Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Menstrual cycle phase effects on nicotine withdrawal and cigarette craving: A review

C. E. Horne, M. J. Carpenter, H. P. Upadhyaya, S. LaRowe, M. Saladin and K. T. Brady, Medical University of South Carolina, Charleston, SC

Review of antidepressant treatment of methamphetamine dependence: Hypothesized mechanisms and future directions

S. Glasner, L. M. Mooney and J. N. Wilkins, Psychiatry, Cedars-Sinai Medical Center, Los Angeles, CA

Symposium III - ADDRESSING ETHNIC DISPARITIES IN DRUG ABUSE TREATMENT

Chairs: Kathleen Carroll and Carmen L. Rosa

MET-S: Design and results of the first multisite substance abuse treatment trial conducted in Spanish

Kathleen Carroll, Yale University School of Medicine, West Haven, CT

American-Indian research challenges

Raymond Daw, University of New Mexico, Na' Nizhoozi Center, Inc., Gallup, NM

Retention of minority subjects in drug abuse treatment research: Evidence from the Clinical Trials Network

Kathryn Magruder, Medical University of South Carolina, Charleston, SC

Healthcare disparities in addiction

Lawrence Brown, Addiction Research and Treatment Corporation, Brooklyn, NY

Discussant

Lula Beatty, National Institute on Drug Abuse, Bethesda, MD

Symposium IV - MEDICATIONS DEVELOPMENT FOR THE TREATMENT OF CANNABIS DEPENDENCE

Chairs: Frank Vocci and Iván D. Montoya

Compounds as probes for cannabinoid receptors

Alex Makriyannis, Northeastern University, Boston, MA

Cannabinoid agonists as treatments for cannabis dependence

Margaret Haney, Columbia University, New York, NY

Safety and efficacy of CB1 antagonists for cannabis dependence

Marilyn Huestis, NIDA/Intramural Research Program, Baltimore, MD

Pharmacotherapy of comorbid cannabis dependence and other psychiatric disorders

Alan I. Green, Dartmouth University, Lebanon, NH

Discussant

Frank Vocci, National Institute on Drug Abuse, Bethesda, MD

Oral Communications 7 - HIV INFECTION AND DRUG-IMMUNE INTERSECTION

Chairs: Toby K. Eisenstein and Sylvia Fitting

Mice become tolerant to morphine-induced depression of NK cell activity: Reinstatement of suppression following withdrawal

A. Verma(1,2), J. J. Meissler(1,2), M. W. Adler(1,3) and T. K. Eisenstein(1,2), (1) Center for Substance Abuse Research, (2) Department of Microbiology and Immunology and (3) Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA

Silencing the PTEN gene reduces striatal neurotoxicity induced by HIV-1 Tat and opiates

T. Y. Zhao, M. H. Adams, S. P. Zou, K. F. Hauser and P. E. Knapp, University of Kentucky, Lexington, KY

Morphine exacerbates HIV-1 Tat-induced neuroinflammation and glial activation in the striatum through CCL2/MCP-1 chemokine-receptor interactions

N. El-Hage, G. Wu, J. Ambati, A. J. Bruce-Keller, P. E. Knapp and K. F. Hauser, University of Kentucky College of Medicine, Lexington, KY

The role of dopaminergic alterations in prepulse inhibition in adult rats following neonatal intracerebral hippocampal gp120 injections

S. Fitting, R. M. Booze and C. F. Mactutus, University of South Carolina, Columbia, SC

Chronic cocaine exacerbates AIDS-related decline in fine motor control in the SIV/Macaque model of AIDS

M. Weed(1,2), D. S. Steward(1), R. A. Cooper(1), S. Perry(1), M. C. Zink(2) and R. D. Hienz(1), (1) Department of Psychiatry and Behavioral Sciences, and (2) Department of Comparative Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Methamphetamine differentially modulates RANTES and its variant allele (In1.1C) gene expression in HIV-1

M. P. Nair, S. D. Mahajan, J. L. Reynolds, S. A. Schwartz and D. E. Sykes, State University of New York at Buffalo, Buffalo, NY

Cocaine and marijuana use: HIV infection and AIDS progression

D. P. Tashkin(1), C. Chao(2), G. C. Baldwin(1), M. D. Roth(1), R. Detels(2) and Z. F. Zhang(2), (1) David Geffen School of Medicine at UCLA, and (2) UCLA School of Public Health, Los Angeles, CA

Inhibition of antibacterial response pathways by THC

G. C. Baldwin, S.M. Kiertscher, S. Uh, K.M. Whittaker, D.P. Tashkin and M.D. Roth, David Geffen School of Medicine at University of California/Los Angeles, Los Angeles, CA

Oral Communications 8 - CANDIDATE MEDICATIONS FOR STIMULANT DEPENDENCE: HUMAN STUDIES

Chairs: William W. Stoops and Frances R. Levin

Bupropion for the treatment of methamphetamine dependence

A. M. Elkashef, R. A. Rawson, E. Smith, A. Anderson, R. Kahn, V. Pierce, S. Li, F. Vocci, W. Ling, W. Haning, M. McCann, J. Mawhinney, J. Campbell, D. Wies, C. Gorodetzky, NIDA/NIH, Bethesda, MD, UCLA, Los Angeles and Matrix Inst. on Addit., Costa Mesa, CA, U. of Missouri, Kansas City, MO and Pacific Addit. Res. Ctr, U. of Hawaii, Honolulu, HI

A double-blind, placebo-controlled assessment of aripiprazole effects on methamphetamine craving: Inpatient longitudinal and cue reactivity studies

M. S. Reid(1), J. Palamar(1), F. Flammino(1), J. J. Mahoney(2), R. De La Garza, II (2), T. Newton(2), A. Elkashef(3), J. Mojsiak(3) and A. Andersen(3), (1) New York University, New York, NY (2) UCLA, Los Angeles, CA and (3) NIDA, Bethesda, MD

Effects of naltrexone on the subjective response to amphetamine in amphetamine-dependent individuals

J. Franck and N. Jayaram-Lindstrom, Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

A low dose of aripiprazole attenuates some of the abuse-related effects of d-amphetamine
W. W. Stoops(1), J. A. Lile(1), P. E. Glaser(2,3,4) and C. R. Rush(1,2,5), (1) Behavioral Science, (2) Department of Psychiatry, (3) Department of Anatomy and Neurobiology, (4) Department of Pediatrics, and (5) Department of Psychology, University of Kentucky, Lexington, KY

N-Acetylcysteine's impact on cocaine-related cues
S. LaRowe(1), P. N. Mardikian(1), P. W. Kalivas(2) and R. J. Malcolm(1), (1) Department of Psychiatry and (2) Department of Neuroscience, Medical University of South Carolina, Charleston, SC

Randomized controlled trial of levodopa-carbidopa and behavior therapy for cocaine-dependent outpatients
J. M. Schmitz(1), M. E. Mooney(2), A. L. Stotts(1), G. F. Moeller(1) and J. Grabowski(1), (1) University of Texas Medical School at Houston, Houston, TX and (2) University of California at San Francisco, San Francisco, CA

Lamotrigine for bipolar disorder and stimulant dependence: A replication and extension study
E.S. Brown, D. Perantie, N. Dhanani, L.B. Beard, P. Orsulak and A.J. Rush, University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Atomoxetine treatment of cocaine-dependent adults with attention-deficit/hyperactivity disorder: An open trial
F. R. Levin(1,2), J. Mariani(1,2), G. Hennessy(2), L. Diaz(2) and D. J Brooks(2), (1) Columbia University, and (2) Substance Abuse, New York State Psychiatric Institute, New York, NY

Symposium V - PARSING THE FUNCTIONS OF DOPAMINE: SELECTIVE RECEPTOR ALTERATIONS
Chairs: James H. Woods and Jonathan Katz

Dopamine D4 receptors: Emerging therapeutic opportunities for novel D4 agonists
Jorge Brioni, Abbott Laboratories, Abbott Park, IL

Drug-induced behavior by lentivirus-mediated local expression changes of D1 and D3 receptors in the mesolimbic dopaminergic pathway
Jean-Luc Dreyer, University of Fribourg, Fribourg, Switzerland

D3-D2 receptor relations in producing behavioral effects in rodents and primates
Gregory Collins, University of Michigan Medical School, Ann Arbor, MI

Revisiting dopamine D1 ligands as candidate medications for psychomotor stimulant abuse
Jack Bergman, Harvard Medical School, Belmont, MA

Discussant
Jonathan Katz, NIDA Addiction Research Center, Baltimore, MD

Oral Communications 9 - CANNABINOIDS IN ACTION
Chairs: Sara Jane Ward and Sandra P. Welch

The CB1 receptor antagonist SR141716 selectively alters extinction of an appetitively conditioned behavior
S. J. Ward and L. A. Dykstra, University of North Carolina at Chapel Hill, Chapel Hill, NC

Chronic administration of 9-THC increases the locomotor-activating effects of cocaine in adolescent but not adult rats
S. Izenwasser, E. Wall and D. Wade, University of Miami School of Medicine, Miami, FL

Detection of cataleptic effects of selective CB2 receptor agonists in rats
P. Little, G. J. Stabely, K. Worm, C. T. Sauei, Q. Zhou and N. Conway-James, Adolor Corporation, Exton, PA

The antinociceptive effect of delta-9-tetrahydrocannabinol in the arthritic rat involves the CB2 cannabinoid receptor
S. P. Welch and M. L. Cox, Virginia Commonwealth University, Richmond, VA

Discriminative stimulus effects of SR 141716A in rhesus monkeys treated with 2 mg/kg/day of Δ9-THC
M.R. Amin and L.R. McMahon, University of Texas Health Science Center
San Antonio, San Antonio, TX

Neurophysiological effects of smoked marijuana during complex cognitive performance
C. L. Hart(1), A. B. Ilan(2), A. Gevins(2), E. W. Gunderson(1), K. Role(2), J. Colley(1) and R. W. Foltin(1), (1) Columbia University, New York, NY and (2) The San Francisco Brain Research Institute and SAM Technology, San Francisco, CA

BOLD imaging of the acute effects of marihuana smoking: Assessing possible confounds due to smoking and global blood flow changes
L. D. Nickerson, J. Theberge, B. Frederick, K. Lindsey and S. Lukas, McLean Hospital, Belmont, MA

Comparison of cannabis and nicotine withdrawal among adults not seeking treatment
A. Liguori(1), C. S. Nave(1), R. G. Vandrey(2) and A. J. Budney(3), (1) Wake Forest University School of Medicine, Winston-Salem, NC, (2) Johns Hopkins University School of Medicine, Baltimore, MD and (3) University of Arkansas for Health Sciences, Little Rock, AR

Oral Communications 10 - PROGRESS IN BUPRENORPHINE TREATMENT

Chairs: Stephen Magura and George E. Woody

Transferring from high doses of methadone to buprenorphine: A randomised trial of three different buprenorphine schedules

N. Clark(1,2,3), N. Lintzeris(5), D. Jolley(4), G. Whelan(3), J. Bell(6), A. Ritter(1) and A. Dunlop(1), (1) Turning Point Alcohol & Drug Centre, (2) Addiction Medicine Unit, Southern Health, (3) Department of Medicine, U. of Melbourne, and (4) Services Research, Monash U., Melbourne, Victoria, Australia; and (5) National Addiction Centre, London, UK

Interaction between buprenorphine and atazanavir

E. McCance-Katz(1), J. R. Baker(1), P. Pade(1), A. Alvanzo(1), R. DiFrancesco(2) and G. D. Morse(2), (1) Virginia Commonwealth University, Richmond, VA and (2) University of Buffalo, Buffalo, NY

Randomized, double blind comparison of drug counseling combined with buprenorphine, naltrexone or placebo for treating opioid dependence and reducing HIV risk in Malaysia

R. S. Schottenfeld(1), M. Mazlan(2) and M. C. Chawarski(1), (1) Yale University, New Haven, CT and (2) Substance Abuse Center, Muar, Malaysia

A trial of integrated buprenorphine/naloxone and HIV clinical care

L. E. Sullivan, B. A. Moore, M. C. Chawarski, J. M. Tetrault, M. V. Pantalon, P. G. O'Connor, R. S. Schottenfeld and D. A. Fiellin, Yale University, New Haven, CT

Emergency department visits involving buprenorphine abuse: 2003-2005

G. E. Woody(1), M. Y. Smith(2) and J. D. Haddox(2), (1) University of Pennsylvania, Philadelphia, PA and (2) Purdue Pharma, L. P., Stamford, CT

Outcomes for buprenorphine maintenance patients in office-based practice

S. Magura(1), S. Whitley(2), S. J. Lee(4), E. Salsitz(3), A. Kolodny(4), T. Taubes(4), R. Seewald(3), H. Joseph(1), D. Kayman(1), C. Fong(1), L. Marsch(1) and A. Rosenblum(1), (1) National Development & Research Institutes, (2) Albert Einstein College of Medicine, (3) Beth Israel Medical Center, New York, NY and (4) Private Practice, New York, NY

Two-year experience with buprenorphine-naloxone for maintenance treatment of opioid-dependence within a private practice setting

J. W. Finch(1) and L. Amass(2), (1) SouthLight, Inc., Durham, NC and (2) Friends Research Institute, Inc., Los Angeles, CA

Evaluation of a buprenorphine training program

E. W. Gunderson(1), D. A. Fiellin(2), F. R. Levin(1), L. E. Sullivan(2) and H. D. Kleber(1), (1) Columbia University, New York, NY and (2) Yale University, New Haven, CT

Symposium VI - EPIDEMIOLOGY OF PRESCRIPTION STIMULANT ABUSE: WHO DOES IT AND WHY?

Chairs: Sean Esteban McCabe and Carol J. Boyd

Risk and protective factors associated with prescription stimulant problem use by adolescents and young adults

Linda Simoni-Wastila, University of Maryland, Baltimore, MD

Characteristics of medical and non-medical users of prescription stimulants

Sean E. McCabe, University of Michigan, Ann Arbor, MI

Secondary and post-secondary students: Motivations to abuse prescription stimulants

Carol J. Boyd, University of Michigan, Ann Arbor, MI

Oral Communications 11 - AN OUNCE OF PREVENTION

Chairs: Andrea L. Stone and Linda B. Cottler

StartSMART: Evaluation of a middle school tobacco prevention program

S.L. Zack(1), Y. H. Wong(1), S. Nemes(2), J. Hoffman(1), J. Weil(2), J. Jones(1), K. Munly (1) and E. Moolchan(3), (1) Danya International, Inc., Silver Spring, MD, (2) Social Solutions International, Olney, and NIDA, Intramural Research Program, Baltimore, MD

Prevention efforts among drug-using American adolescents

D. Lee, Health Care Administration and Public Health, Cleveland State University, Cleveland, OH

Parenting practices and adolescent marijuana involvement: An assessment of first opportunity and first use of marijuana

A. L. Stone(1), H. Chilcoat(2) and N. Ialongo(2), (1) University of Washington, Seattle, WA and (2) Johns Hopkins University, Baltimore, MD

The association between positive and negative ecstasy-related information and college students' future likelihood to use ecstasy

K. Vincent(1), A. Arria(1), K. O'Grady(2), K. Caldeira(1) and E. Wish(1), (1) Center for Substance Abuse Research, and (2) Department of Psychology, University of Maryland, College Park, MD

Pre- and Post-Doc Mixer Salon Princesa

Workshop VI - SOCIETY FOR ADOLESCENT SUBSTANCE ABUSE TREATMENT EFFECTIVENESS (SASATE) 5TH ANNUAL MEETING: NEURO-SCIENTIFIC ADVANCES RELATED TO INTERVENTION

Chairs: Paula Riggs and Laetitia Thompson

Change in diurnal salivary cortisol and serotonin receptors after 16 weeks of combined CBT and fluoxetine/placebo in depressed adolescents with SUD

Paula Riggs, University of Colorado School of Medicine, Denver, CO

Differences in fMRI brain activation patterns on a decision-making task predict one-year treatment outcomes in methamphetamine dependence

Susan Tapert, University of California, San Diego, CA

Preliminary fMRI study of brain activation patterns in response to drug-related stimuli in adolescents before and after 16 weeks of CBT treatment

Laetitia Thompson, University of Colorado School of Medicine, Denver, CO

Society for adolescent substance abuse treatment effectiveness (SASATE) business meeting

Michael L. Dennis, Chestnut Health Systems, Bloomington, IL

Discussant

Nora Volkow, NIDA, Bethesda, MD

Workshop VII - SUBSTANCE ABUSE AND DEPENDENCE IN THE U.S.: CURRENT FINDINGS

Chairs: Deborah Hasin and Bridget Grant

The relationship of substance-specific disorders to specific psychiatric comorbidity

Kevin Conway, NIH/NIDA/DHHS, Bethesda, MD

Changes over time in non-medical use, abuse, and dependence on prescription drugs

Carlos Blanco, Columbia University, New York, NY

Epidemiology of alcohol use disorders in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Bridget Grant, NIAAA, Bethesda, MD

Epidemiology of drug use disorders in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Deborah Hasin, Columbia University/NYS Psychiatric Institute, New York, NY

Discussant

Wilson Compton, NIH/NIDA, Bethesda, MD

Workshop VIII - GLOBAL ADDICTION RESEARCH: ISSUES ON ADDICTION AND HIV/AIDS

Chairs: Joseph E. Schumacher and Gabriele Fischer

HIV risk reduction through treatment: An overview of experience with opioid antagonist therapies in Russia and former Soviet States

George Woody, University of Pennsylvania, Philadelphia, PA

Methamphetamine use in South Africa: Do increased rates of methamphetamine smoking represent an HIV transmission threat?

Richard Rawson, University of California, Los Angeles, CA

Predictors of HIV-HCV status in IDUs in Vinnitsya, Ukraine

Kostyantyn Dumchev, Regional Narcological Dispensary, Vinnitsya, Ukraine

Maintenance treatment and challenges to curb HIV/AIDS in Iran

Azarakhsh Mokri, Tehran University of Medical Sciences, Iranian National Center for Addiction Studies, Tehran, Iran

WHO global research projects on injecting drug use and associated HIV risks

Valdimir Poznyak, WHO, Geneva, Switzerland

Workshop IX - USING MICROARRAYS IN RESEARCH
Chair: David Shurtleff
The nuts and bolts of microarray technology
Dietrich Stephan, Translational Genomics Research Institute, Phoenix, AZ

Workshop X - HTS AND PUBCHEM: NUTS AND BOLTS
Chair: Christine Colvis
How to do high throughput screening
David Weaver, HTS Center, Vanderbilt University, Nashville, TN
How to access and use PubChem
Tudor Oprea, University of New Mexico School of Medicine, New Mexico

Workshop XI - UNDERSTANDING THE PHENOMENON OF OPIOID PRESCRIPTION DRUG ABUSE AND ITS REGULATORY CHALLENGES
Chairs: Deborah Leiderman and Catherine Dormitzer
Prescription drug abuse: Overview and social context
Deborah Leiderman, FDA, Rockville, MD
Findings from the Drug Abuse Warning Network on opioid analgesics
Judy Ball, Office of Applied Studies/SAMHSA, Rockville, MD
Epidemiologic surveys on opioid prescription drug abuse and drug utilization patterns in the United States
Catherine Dormitzer, Office of Drug Safety/FDA, Silver Spring, MD
Challenges from the pain clinician's perspective
Nathaniel Katz, Tufts University School of Medicine, Medford, MA
Beyond scheduling: Managing risks associated with opioid products
Silvia Calderon, FDA, Rockville, MD

Tuesday, June 20, 2006

Early Career Investigator Awards Breakfast

NIDA Forum II - THE NIH ROADMAP: OPORTUNITIES FOR INTER-DISCIPLINARY TRAINING and BEHAVIORAL RESEARCH
Chair: Timothy P. Condon
The NIH Roadmap: Progress and impact on NIDA
Timothy P. Condon, NIDA, Bethesda, MD
Interdisciplinary methods and technology initiative
Lisa Onken, NIDA, Bethesda, MD
Interdisciplinary research training opportunities
TBA, NIDA, Bethesda, MD

Public Policy Forum
BLENDING SCIENCE, PUBLIC POLICY AND ADVOCACY
Chair: William L. Dewey
The politics of science and the science of politics. Federal advocacy in a post-doubling, postsurplus, post-Abramoff world
Ed Long, Capitol Associates, Washington, DC
CPDD public policy activities including Friends of NIDA
William L. Dewey, Medical College of Virginia/Virginia Commonwealth University, Richmond, VA
NIDA's role in educating the public on addiction sciences
Geoff Laredo, NIDA, Bethesda, MD
Communicating the value of the science of drug abuse to the public at large
Martin Iguchi, Rand Corporation, UCLA School of Public Health, Santa Monica, CA

Late-Breaking Research News
Chair: Sharon Walsh

POSTER SESSION III - POLYDRUG ABUSE II

Adult mortality among males with substance use disorders vs. controls

B. M. Martz(1), M. D. Reynolds(1), J. R. Cornelius(1,2) and R. E. Tarter(1), (1) University of Pittsburgh, and (2) Western Psychiatric Institute and Clinic, Pittsburgh, PA

College drug use: Prevalence, patterns, and interest in interventions

R. S. Palmer(1), D. Moreggi(2), B. J. Rounsaville(1) and S. A. Ball(1), (1) School of Medicine, Yale University, and (2) University of New Haven, New Haven, CT

Drug fluency: A potential marker for substance abuse

R. Z. Goldstein(1), P. A. Woicik(1), T. Maloney(1), T. Lukasik(1), N. Alia-Klein(1), G. J. Wang(1), J. S. Fowler(1), C. Wong(1) and N. D. Volkow(2), (1) Brookhaven National Lab, Upton, NY and (2) National Institute on Drug Abuse, Bethesda, MD

Effects of sleep deprivation on cognition, decision-making and impulse control

A. Acheson, J.B. Richards and H. de Wit, University of Chicago, Chicago, IL, and University at Buffalo, State University of New York, Buffalo, NY

Working memory and drug use in methadone clinic patients

G. M. Heyman, McLean Hospital, Belmont, MA

Effect LAAM dose and reducing contingency management rewards on illicit drug use in opioid-dependent cocaine abusers

A. Oliveto(1), J. Poling(2,3) and T. R. Kosten(2,3), (1) Psychiatry, University of Arkansas Medical School, Little Rock, AR, (2) Yale University, New Haven, CT and (3) VA CT Healthcare System, West Haven, CT

Nondisclosure of cannabis use: Predictors and relationship to treatment outcome in methadone-maintained patients

U. E. Ghitza, D. H. Epstein and K. L. Preston, Clinical Pharmacology and Therapeutics Branch, /NIDA/Intramural Research Program/DHHS, Baltimore, MD

Multimodal assessment of reward function in alcohol and heroin dependence

I. Elman(1), D. Ariely(2), N. Mazar(2), M. Tsoi(3), E. Verbitskaya(3), V. Egorova(3), T. Romanova(3), A. Burakov(3), D. Masalov(3), T. Didenko(3), S. Lukas(1), E. Zvartau(3) and E. Krupitsky(3), (1) McLean Hospital, Harvard Medical School, Belmont, MA, (2) MIT, Cambridge, MA and (3) State Pavlov Medical University, St. Petersburg, Russian Federation

Preliminary findings of the WHO ASSIST Phase III study in an Australian setting: A five-minute brief intervention for illicit drugs linked to ASSIST scores

R. Ali, R. Humeniuk and D. Newcombe, University of Adelaide, Adelaide, South Australia

Prevalence and relationship of overweight and obesity among men and women in a long-term residential substance abuse treatment program

L. L. Green(1), T. Horton(2), A. Phillips(2), F. Levin(1) and R. Fullilove(1), (1) Columbia University, and (2) Phoenix House, New York, NY

Individual and social factors associated with drug treatment participation

V. A. Gyarmathy(1,2) and C. A. Latkin(3), (1) Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, (2) National Development and Research Institutes, Inc., New York, NY and (3) Department of Health, Behavior & Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Treatment Cost Analysis Tool (TCAT) for provider estimates of accounting and economic costs

P. M. Flynn(1), A. Beaston-Blaakman(2), K. Broome(1), D. Shepard(3), D. Knight(1) and C. Horgan(3), (1) Texas Christian University, Fort Worth, TX, (2) Family Health International, Research Triangle Park, NC and (3) Brandeis University, Waltham, MA

Impact of behavioral incentives on residential treatment attendance in drug-dependent women

D. Svikis, D. Langhorst, S. Meshberg-Cohen, T. Vance, A. Alvanzo and L. Anderson, Virginia Commonwealth University, Richmond, VA

Salience of follow-up research incentives as a function of magnitude and mode of payment: Generalizability to higher payment magnitudes

J. R. Croft, D. S. Festinger, D. B. Marlowe, A. M. Sauer, K. L. Dugosh and J. M. Caughie, Treatment Research Institute, Philadelphia, PA

Adoption of research-based practices in two randomized clinical trials

J. R. Guydish, S. T. Manser, B. M. Tajima and M. Jessup, University of California, San Francisco, CA

Correlates of long-term recovery after treatment

M. L. Dennis, M. A. Foss and C. K. Scott, Lighthouse Institute, Chestnut Health Systems, Bloomington and Chicago, IL

Prevalence of erectile dysfunction medication use by veterans applying for substance abuse treatment
A. J. Cotton(1,2), K. Horvath(1), C. M. Terry(1,3) and D. A. Calsyn(2,4), (1) Veterans Affairs Puget Sound HCS, (2) Department of Psychiatry & Behavioral Sciences, (3) Department of Psychology, and (4) Alcohol & Drug Abuse Institute, University of Washington, Seattle, WA

Education level: Its impact on questionnaire psychometrics among substance abuse treatment clients
E.M. Bohlig, T.M. Bohman, K. Alanis, M. Steinley-Bumgarner and R.T. Spence, University of Texas, Cedar Creek, and University of Texas System Administration, Austin, TX

Spiritual orientation and engagement in therapeutic community treatment
H. Dermatis, T. James, M. Galanter and G. Bunt, NYU School of Medicine, New York, NY

TREATMENT

Program emphasis on spirituality and adoption of evidence-based practices
J. A. Johnson, L. J. Ducharme, H. K. Knudsen and P. M. Roman, University of Georgia, Athens, GA

The relationship between parental substance abuse and long-term coping in adult domestic violence survivors
S. Griffing, T. Jospitre, M. Chu, R. Sage, L. Madry and B. Primm, Urban Resource Institute, Brooklyn, NY

Live supervision via teleconferencing improves acquisition of MI skills after workshop attendance
J. L. Smith(1), P. C. Amrhein(2), A. C. Brooks(1), K. M. Carpenter(1), D. Levin(1), E. A. Schreiber(1) and E. V. Nunes(1), (1) New York State Psychiatric Institute, New York, NY and (2) Montclair State University, Montclair, NJ

Technology transfer to community-based treatment: Comparison of feasibility and acceptability of context-tailored training vs. standard workshop
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Healthy Lifestyles: A psycho-educational group program for women with substance use disorders
A. Mhaskar, D. L. Miller, A. H. Skinstad and M. Orwa, University of Iowa, College of Public Health, Iowa City, IA

HIV/AIDS II

Hepatitis C status among heroin and cocaine injection drug users: The role of intellectual function deficits
S. G. Severtson and W. W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Prevalence of hepatitis C among a cohort of Hispanic injection drug users
J. Sanchez(1) and C. Rojas(2), (1) Florida International University, and (2) University of Miami, Miami, FL

Prevalence of hepatitis C among injecting drug users in Vinnitsa, Ukraine
R. Soldyshev(1), K. Dumchev(1), J. Schumacher(2) and L. Moroz(1), (1) Infectious Diseases, Vinnitsa National Pirogov Medical University, Vinnitsa, Ukraine and (2) University of Alabama at Birmingham, Birmingham, AL

Rates of HIV, hepatitis A, and hepatitis C among drug users in jail and correctional facilities
A. Lawson, M. Schultz, C. Patterson and W. W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Changes in HCV knowledge and self-efficacy among drug treatment staff in NYC: Preliminary data on the effectiveness of an innovative staff training
S. M. Strauss(1), J. Astone-Twerell(1), C. Munoz-Plaza(1), D. C. Des Jarlais(2), M. Gwadz(1), H. Hagan(1), A. Osborne(1) and A. Rosenblum(1), (1) National Development and Research Institutes, New York, NY and (2) Beth Israel Medical Center, New York, NY

Contribution of the FibroScan® to healthcare access for drug users and precarious population: Observational study
M. Bary, D. Touzeau, K. Asselah, J. Lherm, A. Bendjebbour and A. Boukhemair, Moulin Joly, Paris, and Clinique Liberte, Bagneux, France

How patterns of alcohol use impact physical and mental health in HIV-positive individuals
E. Rosof(1) and J. T. Parsons(2,3), (1) Medical and Health Research Association, (2) Hunter College, City University of New York, and (3) Center for HIV Educational Studies and Training, New York, NY

Communication about condom use and reported condom use among participants enrolled in drug treatment
Y. Song(1,2), D. A. Calsyn(3,4), S. R. Doyle(4), S. Herr(5) and J. L. Sorensen(1), (1) University of California, San Francisco, and (2) San Francisco VA Medical Center, San Francisco, CA; (3) University of Washington School of Medicine, and (4) University of Washington, Seattle, WA; and (5) Compass Recovery Services, Toledo, OH

Sexual practices in methadone maintenance and outpatient psychosocial drug treatment samples
M. Hatch-Maillette(1), D. Calsyn(1,2), S. Doyle(1), A. Woods(3), S. Coyer(4), G. Sillo(5) and G. Woody(2), (1) University of Washington, and (2) University of Washington School of Medicine, Seattle, WA; (3) Compass

Recovery Services, Toledo, OH, (4) Prestera Center, Huntington, WV and (5) UCLA Integrated Substance Abuse Programs, Los Angeles, CA

The context of drug and alcohol use among sex workers in Pretoria, South Africa

W. M. Wechsberg, W. K. Luseno, R. S. Karg and E. Costenbader, RTI International, Research Triangle Park, NC

Rapid assessment of drug use and sexual HIV risk patterns in vulnerable populations in Durban, Pretoria and Cape Town, South Africa

C. D. Parry(1), A. Pluddemann(1), A. Achrekar(2), M. Pule(1), F. Koopman(1), T. Williams(2) and R. Needle(2), (1) Alcohol & Drug Abuse, Medical Research Council, Cape Town, South Africa and (2) Centers for Disease Control & Prevention, Atlanta, GA

Rates of HIV disease among South African drug users: An evaluation of gender and drug use type as HIV risk factors

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Gender differences in sex trade behavior and injection drug use among South African drug users

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Sex under the influence is common for substance abuse treatment patients

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Sexual risk behaviors for HIV transmission in drug user networks in Los Angeles, California

S. Shoptaw(1,3), P. Gorbach(2), C. Hucks-Ortiz(1,3) and S. Larkins(1,3), (1) Department of Family Medicine, (2) Department of Epidemiology, and (3) Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Behavioral functions of sexual behavior across regular, casual, and commercial partners among urban drug users with a history of childhood victimization: Gender and context

M.A. Bornovalova, M. Nock, K. Belendiuk and C.W. Lejuez, University of Maryland, College Park, MD and Harvard University, Cambridge, MA

Sex (trading) in the city: Practices and beliefs among female crack/cocaine sex traders

L. B. Cottler, A. Ben Abdallah and C. Callahan, Washington University School of Medicine, St. Louis, MO

Treatment-related reduction in HIV sexual risk behavior: A CTN secondary analysis

T. K. Killeen(1), R. Carter(1), M. Stitzer(2), G. Woody(3), M. Copersino(4), J. Roll(5) and R. Booth(6), (1) Medical University of South Carolina, Charleston, SC, (2) Johns Hopkins University, Baltimore, MD, (3) U. of Pennsylvania, Philadelphia, PA, (4) McLean/Harvard, Belmont, MA (5) Washington State U., Spokane, WA and (6) U. of Colorado, Denver, CO

Direct and indirect effects of neighborhood disorder on drug use and high-risk sexual partners

C. A. Latkin(1), A. Curry(1), W. Hua(2) and M. Dave(1), (1) Department of Health Behavior & Society, and (2) Department of International Health, Johns Hopkins University, Baltimore, MD

Statistical and spatial analysis of high-risk behaviors among HIV-positives in New York City

M. Pantin, Sociomedical Sciences, Columbia University, New York, NY

PRESCRIPTION DRUG ABUSE

The diversion of prescription opioids in the U.S.

J. Inciardi and H. L. Surratt, University of Delaware, Coral Gables, FL

Relative rate of opioid analgesic abuse in communities in the U.S.

M. Y. Smith(1), W. Irish(2), J. Wang(2), J. D. Haddox(1) and R. Dart(3), (1) Purdue Pharma LP, Stamford, CT, (2) RTI Health Solutions, Research Triangle Park, NC and (3) Rocky Mountain Poison & Drug Center, Denver, CO

Diversion of controlled substances at the pharmacy level: 2005 findings from RxPATROL®

A. Graham, M. Y. Smith and J. D. Haddox, Purdue Pharma LP, Stamford, CT

Trends in nonmedical use of prescription drugs among U.S. college students: Results from four national surveys

S. E. McCabe(1), B. West(1) and H. Wechsler(2), (1) University of Michigan, Ann Arbor, MI and (2) Harvard University, Boston, MA

Adolescent prescription opioid abuse and misuse: Surveillance by poison centers

R. C. Dart(1,2), A. Hughes(1) and M. Y. Smith(3), (1) Rocky Mountain Poison & Drug Center, and (2) University of Colorado Health Sciences Center, Denver, CO and (3) Purdue Pharma, L.P., Stamford, CT

Application of statistical process control methods to monitor emergency department visits involving intentional abuse of OxyContin® or hydrocodone
J. L. Green(1), M. Y. Smith(2) and J. D. Haddox(2), (1) Westat Corporation, Jefferson, MD and (2) Purdue Pharma LP, Stamford, CT

Statistical process control methods for improved signal detection in prescription drug abuse surveillance
S. Butler(1), J. Benneyan(2), N. Katz(1,3), R. Colucci(4), B. Houle(1) and A. Villapiano(1), (1) Inflexxion, Inc., Newton, MA, (2) Northeastern University, and (3) Tufts University School of Medicine, Boston, MA; and (4) Colucci & Associates, LLC, Newtown, CT

Systematic assessment of abuse or diversion in a clinical trial of analgesics
C. Wright, IV, M. A. Zalman, J. D. Haddox, E. D. Kramer, R. D. Colucci and P. D'Ambrosio, Purdue Pharma L.P., Stamford, CT

Pharmacokinetic urine monitoring: A new tool for minimizing trafficking in prescribed opioids
M. J. Kell, Labyrinth Institute, Smyrna, GA

Risk factors associated with non-medical prescription opioid use: Results from a national survey
W. C. Becker, R.A. Desai, J.M. Tetrault, L.E. Sullivan and D.A. Fiellin, Yale University, New Haven, CT

Circumstances associated with risk of abuse of opioids in clinical trials
M. Zalman, C. Wright, IV, E. D. Kramer and J. D. Haddox, Purdue Pharma LP, Stamford, CT

Characterization of individuals who abuse prescription opioid analgesics or heroin
T. J. Cicero(1), J. A. Inciardi(2) and A. Munoz(3), (1) Washington University, St. Louis, MO, (2) University of Delaware, Coral Gables, FL and (3) The Johns Hopkins University School of Public Health, Baltimore, MD

A structured field study assessing the abuse potential of different opioid formulations in Canada
E. M. Sellers(1,3), K. A. Schoedel(1), R. Schuller(1), M. K. Romach(1,3) and G. L. Horbay(2), (1) Ventana Clinical Research Corporation, (2) Janssen-Ortho Inc, and (3) University of Toronto, Toronto, Ontario, Canada

Abuser-reported sources of illegally obtained opioid analgesic medications
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Role of the therapeutic alliance in the treatment of pain patients who abuse prescription opioids
A. Bethea, M. Acosta and D. L. Haller, St. Luke's-Roosevelt Hospital, New York, NY

PERINATAL DRUG EXPOSURE

The bed nucleus of stria terminalis as a neural substrate for mediating opiate withdrawal in neonatal rats
K. A. Richardson(1), A. V. Mason(1,2), S. D. Kwak(1), G. L. McLemore(1,2) and E. B. Gauda(1), (1) Johns Hopkins Hospital, and (2) Morgan State University, Baltimore, MD

Maternal blood and organ toluene levels after acute and repeated binge exposures
J. Batis, S. Irtenkauf, J. Hannigan and S. Bowen, Wayne State University, Detroit, MI

Effects of chronic methamphetamine use in the pregnant rat and her litter
S. J. White, E. M. Laurenzana and S. M. Owens, University of Arkansas for Medical Sciences, Little Rock, AR

Effects of prenatal exposure to nicotine on locomotor activity in pre-weanling rats
M. G. LeSage(1,2), E. Gustaf(1), M. Dufek(1) and P. R. Pentel(1,2), (1) Minneapolis Medical Research Foundation, and (2) University of Minnesota Medical School, Minneapolis, MN

Chronic exposure to analgesic doses of oxycodone does not alter female reproductive function in rats
V. Batra, L.M. Franklin and L. Schrott, LSU Health Sciences Center, Shreveport, LA

Early smoking status predicts smoking-cessation outcomes in pregnant women
S. Higgins(1,2), S. H. Heil(1,2), L. J. Solomon(2), I. M. Bernstein(3), A. M. Dumeer(1) and C. S. Thomas(4), (1) Department of Psychiatry, (2) Department of Psychology, (3) Department of Obstetrics & Gynecology, and (4) Department of Biostatistics, University of Vermont, Burlington, VT

The influence of cigarette smoking in opioid-maintained pregnant women
University of Vienna, and (2) University of Vienna, Vienna, Austria

Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women
J. H. Yoon(1), S. T. Higgins(1,2), S. H. Heil(1,2), C. S. Thomas(3) and R. J. Sugarbaker(1), (1) Department of Psychiatry, (2) Department of Psychology, and (3) Department of Biostatistics, University of Vermont, Burlington, VT

Tobacco use in a residential sample of drug-dependent women
L. M. Anderson, D. Svikis, D. Langhorst and S. Meshburg-Cohen, Virginia Commonwealth University, Richmond, VA

Weight gain following smoking cessation among female prisoners

K. Cropsey(1), S. Ceperich(2), M. Weaver(1), G. Villalobos(1) and M. Stitzer(3), (1) Virginia Commonwealth University, Richmond, VA, (2) University of Virginia, Charlottesville, VA and (3) Johns Hopkins University, Baltimore, MD

Smoking initiation among alcohol-dependent men referred to substance abuse treatment after a domestic violence arrest

T. P. George, C. J. Easton, and A. Weinberger, Yale University, New Haven, CT

Reinforcement-based Treatment is an effective treatment for drug dependence during pregnancy

M. Tuten and H. E. Jones, School of Medicine, Johns Hopkins University, Baltimore, MD

Leveraging technology: Evaluation of a computer-based brief intervention for postpartum drug use and a dynamic predictor of treatment response

S. J. Ondersma(1), D. S. Svikis(2) and C. R. Schuster(1), (1) Wayne State University, Detroit, MI and (2) Virginia Commonwealth University, Richmond, VA

Association between drug abuse and spontaneous or threatened miscarriage in psychiatrically ill women

K. Peindl(1), P. Mannelli(1), T. Lee(1), C. Kuhn(1), M. Narasimhan(2), R. Hubbard(1), K. Hill(3) and A. Patkar(1), (1) Duke University, Durham, NC (2) University of South Carolina, Columbia, SC and (3) Yale University, New Haven, CT

Prevalence and correlates of substance use during pregnancy: Results from a national sample

J. R. Havens(1), L. A. Simmons(2), W. F. Hansen(3) and C. G. Leukefeld(1), (1) Center on Drug and Alcohol Research, (2) Department of Family Studies, and (3) Department of Obstetrics and Gynecology, University of Kentucky, Lexington, KY

Childhood abuse, substance use disorder, and pregnancy problems in young adult women

A. C. Mezzich, M. Swaney, J. Heliste and B. Day, University of Pittsburgh, Pittsburgh, PA

Factors associated with health status—10-year follow-up of prenatal cocaine/polydrug use

S. Minnes, L. Singer and S. Satayathum, Case Western Reserve University, Cleveland, OH

Examiner-rated behavior in male and female children with in utero cocaine exposure

V.H. Accornero, L. Xue, C.E. Morrow, M.W. Stuhlman, J.C. Anthony, C.B. McCoy and E.S. Bandstra, University of Miami Miller School of Medicine, Miami, FL, and Michigan State University, East Lansing, MI

Teacher report of aggressive behaviors in prenatally cocaine-exposed and non-cocaine-exposed children at 9 years of age

T. L. Scott(1), E. J. Short(1), S. Satayathum(2), H. L. Kirchner(2), S. Minnes(3) and L. T. Singer(2,3), (1) Department of Psychology, (2) Department of Pediatrics, and (3) Department of General Medical Sciences, Case Western Reserve University, Cleveland, OH

Vagal tone during sustained attention tasks among 8-year-olds prenatally exposed to cocaine

J. A. Kable(1), C. D. Coles(1,2), M. E. Lynch(2) and K. A. Platzman(2), (1) Department of Pediatrics and (2) Department of Psychiatry, Emory University School of Medicine, Atlanta, GA

Cocaine decreases progesterone synthesis in placental cells and elevates prostaglandin levels in the amniotic fluid during pregnancy in humans

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Methadone concentrations in breast milk and blood and associated neonatal neurobehavior

L. M. Jansson(1), R. Choo(2), M. Velez(1), C. Harrow(3), J. Schroeder(4) and M. Huestis(2), (1) The Johns Hopkins University School of Medicine, (2) NIH/NIDA/Intramural Research Program, (3) Johns Hopkins Bayview Medical Center and (4) Office of the Clinical Director, NIH/NIDA/Intramural Research Program, Baltimore, MD

COCAINE, AMPHETAMINES: HUMAN STUDIES II

A quasi-experimental evaluation of employment-based reinforcement of cocaine and opiate abstinence in unemployed community methadone patients

W. D. Donlin, T. Knealing, M. Needham, K. Kolodner, M. Fingerhood, C. J. Wong and K. Silverman, Johns Hopkins University School of Medicine, Baltimore, MD

Therapeutic alliance with research assistants and with counselors among methadone maintenance patients receiving an abstinence-based reinforcement intervention in a community

L. A. Benishek(1,2), S. E. Shealy(1), B. J. Rosenwasser(1), M. L. Kerwin(1,3) and K. C. Kirby(1,2), (1) Behavioral Interventions, Treatment Research Institute, (2) University of Pennsylvania School of Medicine, Philadelphia, PA and (3) Rowan University, Glassboro, NJ

Crack-using African-American moms: Is parenting a barrier to seeking treatment?

W. K. Lam, W. M. Wechsberg, R. S. Karg, W. A. Zule, R. G. Bobashev and R. Middlesteadt-Ellerson, RTI International, Research Triangle Park, NC

Ethnic disparities in the utilization of treatment services among Proposition 36 clients

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Individual variability in addiction profiles: Importance for medications development

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Sexual and physical abuse in childhood and victimization in adulthood among substance-using women

K. Vaddiparti, A. Ben Abdallah, C. Callahan and L. B. Cottler, Washington University School of Medicine, St. Louis, MO

Risk behaviors of out-of-treatment cocaine base paste and cocaine hydrochloride users: One-year follow-up

R. Santis(1), C. G. Hidalgo(2), J. Rodriguez(3), V. Hayden(1), E. Anselmo(1), R. Torres(1), F. Cartajena(1), J. Dreyse(1), L. Toro(1) and M. J. Jimenez(1), (1) Department of Psychiatry, (2) School of Psychology, Pontificia Universidad Catolica de Chile, and (3) Universidad de Chile, Santiago, Chile

Decision-making deficits and social adjustment impairments in Brazilian crack cocaine users

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Brazilian female crack users show high serum aluminum levels

F. Pechansky(1), F. Kessler(1), L. V. Diemen(1), D. Bumaguin(1), H. Surratt(2) and J. A. Inciardi(2), (1) Center for Drug and Alcohol Research, UFRGS, Porto Alegre, RS, Brazil and (2) Center for Drug and Alcohol Studies, Coral Gables, FL

Life areas with more necessity of change for the improvement of quality of life among cocaine users

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Quality of life in methamphetamine users

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Chronic disorder of mental health and social life due to methamphetamine abuse

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Trends in methamphetamine drug seizures in Canada

B. Brands(1,2,3), K. Richard(1), and R. Hanson(1), (1) Office of Research & Surveillance, DSCS, Health Canada, Ottawa, (2) Clinical Research, Centre for Addiction & Mental Health, Toronto, and (3) University of Toronto, Toronto, Ontario, Canada

The manufacture and sale of methamphetamine

M. P. Hillhouse, P. Marinelli-Casey and R. Rawson, UCLA Integrated Substance Abuse Program, Los Angeles, CA

Is methamphetamine addiction too difficult to treat?

D. A. Crevecoeur and R. Rawson, UCLA, Los Angeles, CA

12-Step participation of methamphetamine-dependent adults previously participating in the Methamphetamine Treatment Project

P. Marinelli-Casey, M. P. Hillhouse and R. Rawson, UCLA Integrated Substance Abuse Program, Los Angeles, CA

Effects of acute d-amphetamine on measures of mood, attention, risk-taking and behavioral inhibition in healthy human volunteers

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Estradiol modulation of the behavioral effects of d-amphetamine in premenopausal women

S. Babalonis, J.A. Lile, C.S. Emurian, S.L. Kendall, C.A. Martin and T.H. Kelly, University of Kentucky, Lexington, KY

Abuse liability of intravenous L-lysine-d-amphetamine (NRP104)

D. R. Jasinski(1) and S. Krishnan(2), (1) Medicine, Johns Hopkins University, Baltimore, MD and (2) New River Pharmaceuticals Inc., Blacksburg, VA

Neurotensin and metenkephalin levels are altered in several brain regions in methamphetamine addicts

P. Frankel(1), M. E. Alburges(1), L. Bush(1), G. R. Hanson(1) and S. J. Kish(2), (1) University of Utah, Salt Lake City, UT and (2) University of Toronto, Toronto, Ontario, Canada

COCAINE, AMPHETAMINES: MECHANISMS AND BEHAVIOR II

Cell cycle events associated with METH-induced astrogliosis

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Methamphetamine-induced neurotoxicity: Deficits in consolidation of Pavlovian conditioning are ameliorated by N-acetylcysteine but not D1 and D2 dopamine receptor agonists

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Effect of naltrexone on amphetamine-induced conditioned place preference

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Differences among inbred rat strains in novelty seeking, locomotor activity and amphetamine self-administration

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Electrophysiology of the medial prefrontal cortex in the behaving rat: Studies of acute and chronic amphetamine treatment

J. J. Stanis and J. M. Gulley, University of Illinois, Urbana-Champaign, Champaign, IL

Discriminative stimulus properties of cocaine in rats with individual differences in cocaine-induced locomotor activity

J. M. Gulley and D. A. Klein, University of Illinois, Champaign, IL

The effects of aerobic exercise on sensitivity to cocaine

M. A. Smith, S. R. Gergans, J. C. Iordanou and M. A. Lyle, Davidson College, Davidson, NC

Effectiveness of cocaine esterase against cocaine-induced convulsions and lethality in mice

M.C. Holden Ko(1), L. Bowen(1), D. Narasimhan(1), N. Lukacs(2), R. Sunahara(1) and J. Woods(1), (1) Department of Pharmacology, and (2) Department of Pathology, University of Michigan, Ann Arbor, MI

A comparison of Lewis and Fischer rat strains on an animal model of drug abuse: Autoshaping (sign-tracking)

D. N. Kearns, M. A. Gomez-Serrano, S. J. Weiss and A. L. Riley, American University, Washington, DC

Temporal discounting of cocaine as a reinforcer by rhesus monkeys

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Effects of repeated cocaine on impulsivity in rats

E. C. Stoffel, R. G. Stutz and K. A. Cunningham, Center for Addiction Research, University of Texas Medical Branch, Galveston, TX

Activation of single neurons in the orbitofrontal cortex during cocaine self-administration

D. E. Moorman(1), A. V. Kravitz(2) and L. L. Peoples(1,2), (1) University of Pennsylvania, and (2) University of Pennsylvania Medical School, Philadelphia, PA

Assessment of extended-access cocaine self-administration on drug intake and breakpoints maintained by food and cocaine in the LEW rat strain

K. B. Freeman, D. N. Kearns, S. J. Kohut and A. L. Riley, American University, Washington, DC

Reinforcement history determines the reinforcing effects of quinpirole in the rat

G. T. Collins and J. H. Woods, University of Michigan Medical School, Ann Arbor, MI

Maternal separation causes changes in cocaine self-administration in dams and treated pups as adults

M. Moffett(1), J. Harley(1), D. Francis(3), S. Sanghani(2), W. Davis(2) and M. Kuhar(1), (1) Emory University, Atlanta, GA, (2) Indiana University School of Medicine, Indianapolis, IN and (3) University of California Berkeley, Berkeley, CA

ADOLESCENT DRUG ABUSE I

Pre-adolescent phenylpropanolamine produces persistent perturbations in accumbens monoaminergic and amino acid transmission: Implications for cocaine addiction

K. K. Szumlinski, A. Liu and K. D. Lominac, University of California, Santa Barbara, Santa Barbara, CA

Adolescents sensitize more than adults to a single high dose of cocaine

J. Caster, Q. D. Walker and C. M. Kuhn, Duke University Medical Center, Durham, NC

Disruption of the neuronal nitric oxide synthase gene prevents neuroadaptations involved in the maintenance and reinstatement of cocaine conditioned place preference in adolescent mice

M.A. Balda, K.L. Anderson and Y. Itzhak, University of Miami School of Medicine, Miami, FL

Conditioned taste aversion to a variety of substances is reduced in adolescents compared to adults

N. L. Schramm-Sapyta, S. Chaudhry and C. M. Kuhn, Duke University, Durham, NC

Early adolescent THC alters behavior in avoidance paradigms in sex-specific ways

D. Dow-Edwards, N. Zhao and S. Stephenson, State University of New York-Downstate, Brooklyn, NY

High-risk drinking, substance use, and risk behavior among college students: A preliminary investigation

K. Ragsdale(1), C. Gore-Felton(2) and E. McGarvey(3), (1) National Development and Research Institutes, New York, NY (2) Stanford University, Stanford, CA and (3) University of Virginia, Charlottesville, VA

Distress tolerance as a predictor of adolescent substance use

S. B. Daughters(1), C. W. Lejuez(1), M. N. Danielson(2), M. N. Sargeant(1), E. K. Reynolds(1), M. A. (1) and D. Schulzinger(1), (1) University of Maryland, College Park, MD and (2) Medical University of South Carolina, SC

Violence exposure, coping processes, and drug and alcohol use in early adolescence

W. Kliewer and K. Reid-Quinones, Virginia Commonwealth University, Richmond, VA

Project Youth Connect of northern Colorado-expanded: A rural adolescent drug prevention, mentoring program

K. Zavela Tyson, D. J. Benavides and K. McGill, University of Northern Colorado, Greeley, CO

Using nonlinear mixed models to analyze discounting behavior in adolescent substance users and controls

S. K. Mikulich-Gilbertson, L. L. Thompson, K. M. Raymond, S. K. Stover and T. J. Crowley, University of Colorado, Denver, CO

Question-based assessments of delay discounting: Do respondents spontaneously incorporate uncertainty into their valuations for delayed rewards?

B. Reynolds, M. Patak and P. Shroff, The Ohio State University, Columbus, OH

Delay discounting and teen smoking

M. Patak, P. Shroff and B. Reynolds, The Ohio State University, Columbus, OH

Alcohol use and body image among adolescent experimental smokers

S. B. Pierotti(1), M. L. Magee(1), C. Heckman(2) and K. S. Ingersoll(3), (1) Institute for Drug and Alcohol Studies, (2) Department of Psychiatry, Virginia Commonwealth University, Richmond, and (3) University of Virginia, Charlottesville, VA

Menstrual symptomatology and cigarette smoking in adolescent girls: Preliminary findings

M. Jaszyna-Gasior, F. H. Franken, M. K. Leff, K. S. Bagot, E. J. Luther, M. B. Royo, C. C. Collins, E. D. Thorner and E. T. Moolchan, Teen Tobacco Addiction Research Clinic and, DHHS, NIH/NIDA/Intramural Research Program, Baltimore, MD

Gender differences in smoking expectancies and the relationship of expectancies to amount of smoking

A. H. Weinberger(1,2), E. Reutenauer(1), J. C. Vessicchio(1) and T. P. George(1), (1) Yale University School of Medicine, New Haven, CT and (2) VISN1/MIRECC, West Haven VA, West Haven, CT

Marijuana use and tobacco smoking trajectory: Associated ethnic and gender differences among adolescent smokers

E. T. Moolchan, F. H. Franken, C. C. Collins, E. J. Luther, S. J. Heishman, D. H. Epstein and M. Jaszyna-Gasior, NIH/NIDA/Intramural Research Program, Baltimore, MD

Gender differences in the efficacy of intervention trials on preventing tobacco smoking among children and adolescents

Y. Wang(1), N. Ialongo(2), F. A. Wagner(1), S. F. Lambert(3), C. L. Storr(2) and D. C. Browne(1), (1) Morgan State University, and, (2) Johns Hopkins University, Baltimore, MD and (3) George Washington University, Washington, DC

Adolescent and parent agreement of withdrawal symptoms of youth enrolled in a Baltimore tobacco cessation research program

E. D. Thorner, M. Jaszyna-Gasior, J. R. Schroeder and E. T. Moolchan, NIH/NIDA/Intramural Research Program, Baltimore, MD

Tobacco and marijuana blunt smoking effects on spirometric measures; Preliminary findings

M. Royo, M. Jaszyna-Gasior, M. K. Leff, E. J. Luther, K. S. Bagot, E. D. Thorner and E. T. Moolchan, NIH/NIDA/Intramural Research Program, Baltimore, MD

Does working increase the risk of adolescent tobacco use? An epidemiologic investigation

R. Ramchand, H. D. Chilcoat and N. S. Ialongo, Johns Hopkins University, Baltimore, MD

Patient commitment language in response to a projective narrative predicts length of stay in a residential treatment program

M. Janoff(1), P. Amrhein(2), J. Wilson(1) and E. V. Nunes(1), (1) New York State Psychiatric Institute, Columbia University, New York, NY and (2) Montclair State University, Montclair, NJ

Characteristics and life history of opioid-dependent adolescents

L. Marsch(1,2), E. Cavell(2), W. K. Bickel(3) and G. J. Badger(4), (1) National Development and Research Institutes, and (2) St. Luke's-Roosevelt Hospital, New York, NY; (3) University of Arkansas for Medical Sciences, Little Rock, AR and (4) University of Vermont, Burlington, VT

Polydrug use as a risk factor for attempted suicide among adolescents in Puerto Rico

J. C. Reyes, R. Robles, H. Colon, J. Negron, C. Marrero, T. Matos, J. Calderon and O. Perez, Universidad Central del Caribe, Bayamon, Puerto Rico

Spirituality and its relationship to substance use and comorbid conditions in an ethnically diverse adolescent treatment population

J. C. Titus and M. L. Dennis, Chestnut Health Systems, Bloomington, IL

Non-medical prescription drug use among young injection drug users

S. Lankenau(1,2), B. Sanders(1,2), J. Bloom(2) and D. Hathazi(2), (1) University of Southern California, and (2) Childrens Hospital Los Angeles, Hollywood, CA

PROGRAM DESCRIPTION

The French cannabis policy

C. Gatignol, F. Lert and D. Jayle, MILDT, Paris, France

Cannabis Info Service: Part of the French cannabis programme

D. Jayle(1), B. Cohen(2) and C. Gatignol(1), (1) MILDT, and (2) DATIS, Paris, France

Cannabis clinics: Part of the French cannabis policy 144

M. Chedru(1), C. Bernard(2), C. Gatignol(1), O. Middleton(1), J. M. Costes(3) and D. Jayle(1), (1) MILDT, Paris, (2) Ministry of Health, Paris, and (3) FMCDDA

Developing a multi-problem screening system for youth

K. A. Munly(1), L. S. Hess(1), S. Libretto(1), Y. H. Wong(1), J. Sexton(1), J. Jones(1) and E. Moolchan(2), (1) Danya International, Inc., Silver Spring, and (2) DHHS/NIH/NIDA Intramural Research Program, Baltimore, MD

High school and community health prevention program in Guadalajara, Jalisco

J. A. Gutierrez-Padilla(1,3), M. LA Torre-Gutierrez(1), A. Campos-Sierra(1), M. Mendoza- Garcia(1), L. Alcala-Padilla(1), O. Campollo-Rivas(1,2), (1) Hospital Civil De Guadalajara, (2) Universidad De Guadalajara, Guadalajara, and (3) Fundacion Hospitales Civiles De Guadalajara, Guadalajara, Jalisco, Mexico

Combined substance use and HIV prevention for incarcerated adolescents

D. W. Watson(1,2), M. Mouttapa(1,2), J. Kavich(1,2), W. J. McCuller(1,2), A. C. Rossi(1,2), L. Francis(1,2) and E. Nieves(1,2), (1) Friends Research, Torrance, and (2) Integrated Substance Abuse Program, UCLA, Los Angeles, CA

HIV and substance use prevention for male adolescent detainees

J. Kavich(1,2), M. Mouttapa(1,2), W. J. McCuller(1,2), D. W. Watson(1,2), A. C. Rossi(1,2), L. Francis(1,2) and E. Nieves(1,2), (1) Friends Research, Torrance, and (2) Integrated Substance Abuse Program, UCLA, Los Angeles, CA

Risky business: Sexual behaviors, drug use and violence among sex-trading women in St. Louis

T. A. Millay, C. Callahan and L. Cottler, Washington University School of Medicine, St. Louis, MO

Challenges of recruiting high-risk drug-using women for a HIV vaccine trial

H. Navaline, J. Becher, M. Lanier, T. Brown, R. White, G. Woody and D. Metzger, University of Pennsylvania, Philadelphia, PA

Selectively willing: Attractions and barriers to HIV vaccine research participation among crack-cocaine-using women in Philadelphia

C. D. Voytek, K. T. Jones, T. Brown, R. White, A. Fleck, G. E. Woody and D. S. Metzger, School of Medicine, University of Pennsylvania, Philadelphia, PA

One stop shop: A model of integrated antiviral and substance dependence treatment for injecting drug users

N. M. Walsh(1,2), A. J. Dunlop(1), J. Kelsall(3), P. Spry-Bailey(1) and N. J. Crofts(1), (1) Turning Point Alcohol and Drug Centre, Fitzroy, (2) Macfarlane Burnet Institute for Medical Research and Public Health, and (3) VIVAIDS, North Melbourne, Victoria, Australia

A prospective, multicenter, observational study on compliance to hepatitis C treatments (CHEOBS): Characteristics of HCV-infected patients with psychiatric disorders

J. Lang(2) and P. Melin(1), (1) Chg St Dizier, Saint Dizier, and (2) Ch Erstein, Erstein, France

A prospective French multicenter observational study on compliance to hepatitis C treatments Characteristics of subpopulation of patients who acquired HCV infection via drug abuse

P. Melin(1), J. Lang(2), L. Cattan(3), D. Ouzan(4), M. Chousterman(5) T. Fontanges, P. Marcellin(3) and P. Cacoub, (1) Chg St Dizier, Saint Dizier, (2) Ch Erstein, Erstein, (3) Hopital Beaujon, Clichy, (4) Institut A Tzanck, St Laurent Du Var, and (5) CH Creteil, Creteil, France

Implementation of an electronic information system to enhance practice at an opioid treatment program

L.S. Brown, Jr., S.A. Kritz, M. Chu, C. Madray and C. John-Hull, ARTC, Brooklyn, NY

City-wide evaluation of interim methadone maintenance

D. A. Highfield(1), R. Schwartz(1), B. Das(1) and J. H. Jaffe(1,2), (1) Friends Research Institute, and (2) University of Maryland School of Medicine, Baltimore, MD

Providing integrated office-based methadone treatment in public health medical settings: Experiences and findings from the San Francisco Office-Based Opiate Pilot Program evaluation

D. Hersh(1,2), A. Gleghorn(1), B. Shapiro(2) and C. Simons(1), (1) Community Behavioral Health Services and Department of Public Health, and (2) UCSF, San Francisco, CA

Integrating evidence-based counseling with routine buprenorphine treatment for opiate dependence

F. Altice, M. Copenhaver and R. Bruce, University of Connecticut, Storrs, and Yale University AIDS Program, New Haven, CT

Adherence to a 30-day buprenorphine detoxification in a public program

S. D. King(1), B. S. Brown(1,3), R. P. Schwartz(1), D. Gandhi(2), W. Barksdale(2), E. Weintraub(2) and E. C. Katz(1), (1) Friends Research Institute, and, (2) University of Maryland, Baltimore, MD and (3) University of North Carolina, Wilmington, NC

Evaluation for severe mental illness in buprenorphine maintenance therapy

R. Bruce, L. Chwastiak, F. Altice and M. Copenhaver, Yale University, New Haven, CT

Buprenorphine-assisted treatment in a drug court program

G. L. Rhodes, C. L. Madeja, P. Smith, T. D. Sheehy and C. R. Schuster, Wayne State University, Detroit, MI

Improving treatment participation on parole: The CJ-DATS Transitional Case Management Study

M. Prendergast and J. Cartier, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA

Collaborating with Atlanta-based African-American churches: A promising means for providing Peer-led Addiction Recovery Support Services to inner-city substance users

D. L. Whiters, (1) University of Georgia, Athens, GA, (2) Recovery Community Services Program, Center for Substance Abuse Treatment, Rockville, MD and (3) Recovery Consultants of Atlanta, Inc., Atlanta, GA

Developing a training program that helps counselors become effective leaders of substance abuse treatment facilities

J. E. Sexton(1), S. Libretto(1), H. Wong(1), T. Durham(2) and E. Moolchan(3), (1) Danya International, Inc., and, (2) Danya Institute, Silver Spring, MD and (3) HHS/NIH/NIDA

Worksite wellness health promotion: A toolkit for employers and employees

J. Jones(1), S. Zack(1), Y. H. Wong(1), K. Munly(1) and E. Moolchan(2), (1) Danya International, Inc., Silver Spring, MD and (2) NIH/NIDA/Intramural Research Program, Baltimore, MD

Addiction treatment workforce characteristics for California, Arizona, and New Mexico: Implications for workforce development

T. E. Freese(1,2), M. E. Shafer(1,3) and R. A. Rawson(1,2), (1) Pacific Southwest ATTC, and (2) Integrated Substance Abuse Programs, UCLA, Los Angeles, CA and (3) University of Arizona, Tucson, AZ

Knowledge of and attitudes toward addictive behaviors by student personnel in the upper Midwest states

A. H. Skinstad, A. B. Wallis, M. Wallis and K. Mercer, University of Iowa, College of Public Health, Iowa City, IA

Hand-in-Hand Program: A psycho-educational group program for women with substance use and co-occurring mental health disorders

D. L. Miller, A. H. Skinstad and A. Mhaskar, University of Iowa, College of Public Health, Iowa City, IA

Social and psychological daily contexts of regular alcohol use

N. Chakroun(1), P. M. Llorca(2), P. Chambres(1) and H. Upadhyaya(3), (1) LAPSCO and (2) Psychiatry Unit of CHU, Clermont-Ferrand, France and (3) Medical University of South Carolina, Charleston, SC

School-based ecstasy and related drugs education in Australia: A qualitative study

C. Finney-Lamb, J. Copeland, and P. Dillon, University of NSW, Sydney, New South Wales, Australia

The effect of MDMA administration in human brain measured by 31P MRS

Y. H. Sung, E. J. Jensen, B. J. Dunn and P. F. Renshaw, McLean Hospital, Belmont, MA

Current drug scheduling reviews reported by the Drug Enforcement Administration

S. R. Tella, J. M. Tolliver, G. K. Feussner, B. A. Hayes, S. M. Carr and C. A. Sannerud, Drug Enforcement Administration, Washington, DC

Demonstration of the feasibility of real-time, product-specific, prescription opioid abuse surveillance: The NAVIPPRO system

A. Villapiano(1), S. Butler(1), S. Budman(1), A. Licari(1), L. Morrison(1), K. Lioy(1), B. Houle(1), R. Colucci(2) and N. Katz(1,3), (1) Inflexxion, Inc., Newton, MA (2) Colucci & Associates, LLC, Newtown, CT and (3) Tufts University School of Medicine, Boston, MA

Simulating the operation of a local heroin market: New uses for ethnographic research

L. D. Hoffer(1) and J. Thorp(2), (1) Washington University School of Medicine, St. Louis, MO and (2) The RedFish Group, Santa Fe, NM

Research participant recruitment program for drug abuse studies at NIDA-IRP
J. M. Hess, J. R. Schroeder, M. K. Leff and C. S. Contoreggi, Office of the Clinical Director, National Institute on Drug Abuse-Intramural Research Program, Baltimore, MD
Developing training modules and other tools for international drug abuse researchers
C. Argueta(1), S. Libretto(1), J. Harris(2), J. Jones(1), H. Wong(1), S. Nemes(3) and E. Moolchan(4), (1) Danya International, Silver Spring, MD, (2) Medical Directions, Tucson, AZ, (3) Social Solutions International, Olney, and (4) NIH/NIDA Intramural Research Program, Baltimore, MD
Developing a mental health screening instrument for substance abuse treatment
S. Libretto(1), J. Sexton(1), K. Munly(1), H. Wong(1), S. Nemes(2) and E. Moolchan(3), (1) Danya International, Silver Spring, (2) Social Solutions International, Olney, and (3) HHS/NIH/NIDA/Intramural Research Program, Baltimore, MD
Clearing the murkiness of designing, creating, and checking scoring algorithms
M. S. Fague, A. Ben Abdallah and L. Cottler, Washington University, School of Medicine, St. Louis, MO

Grant-Writing Workshop
Chair: Suman Rao-King

Workshop XII - LONGITUDINAL ANALYSES OF DRUG USE and TREATMENT UTILIZATION—ISSUES, METHODS, EXAMPLES
Chairs: Mary-Lynn Brecht and Yih-Ing Hser

Workshop XIII - NIDA MEDICATIONS WORKSHOP: NEW OPPORTUNITIES FOR CHEMISTS AND PHARMACOLOGISTS
Chair: Nora Chiang
Introduction
Nora Chiang, NIDA, Bethesda, MD
The evolution of NIDA's medications discovery programs
David McCann, NIDA, Bethesda, MD
New molecular targets as potential pharmacotherapies for drug addiction
Jane B. Acri, NIDA, Bethesda, MD
NIDA resources supporting medications discovery and development
Ming Shih, NIDA, Bethesda, MD
Discussant
Rik Kline, NIDA, Bethesda, MD

Workshop XIV - HOW CAN WE BETTER NURTURE THE SUBSTANCE ABUSE COUNSELING WORKFORCE?
Chairs: Anne Helene Skinstad and Ken Winters
Substance abuse counselors' attitudes towards adoption of evidence-based practices
Anne H. Skinstad, University of Iowa, Iowa City, IA
Orientations toward innovations among substance abuse counselors
Paul Roman, University of Georgia, Atlanta, GA
Who will deliver evidence-based treatments: A constructive look at the addiction treatment workforce?
Thomas McLellan, Treatment Research Institute, Philadelphia, PA
Gender and the substance abuse treatment workforce: Implications for the field
Nancy Roget and Susan Storti, University of Nevada, Reno, Nevada and Brown University, Providence, RI
Discussant
Ken Winters, University of Minnesota Medical School, Minneapolis, MN

Workshop XV - JOB INTERVIEWS: TIPS, TRICKS, AND TRAPS
Chairs: Mark Swieter, Teri Levitin, and Mark R. Green
Panelists: Linda Cottler, PhD (Washington University, St. Louis)
Barry Hoffer, MD, PhD (NIDA IRP)
MaryJeanne Kreek, MD (Rockefeller University)
Jim Smith, PhD (Wake Forest University)

Wednesday, June 21, 2006

Animals in Research Forum
Chair: Nancy K. Mello
Speaking for research: Lessons from the frontliners
Jacquie Calnan, President, Americans for Medical Progress

President's Lecture
Neural circuits recruited by drug and food cues: A molecular and systems analysis
Anne E. Kelley, University of Wisconsin, Madison, WI

POSTER SESSION IV - SEX DIFFERENCES
Gender differences in temporal discounting may explain patterns of drug abuse
B. P. Kowal, K. M. Gatchalian, R. Yi and W. K. Bickel, University of Arkansas for Medical Sciences, Little Rock, AR
Gender differences in the pattern and predictors of the cycle of relapse, treatment re-entry and recovery
C. K. Scott(1), M. A. Foss(1), C. Grella(1,2) and M. L. Dennis(1), (1) Chestnut Health Systems, Chicago and Bloomington, IL and (2) University of California, Los Angeles, CA
A gender perspective on violent behaviors in cocaine addicts
J. Gomez(1), S. Tortajada(1), E. Clari(1), A. Saiz(1), J. C. Valderrama(1), I. Serra(1), J. Guillot(2), J. C. Perez de los Cobos(3) and P. Needle(4), (1) Instituto de Historia de la Ciencia y Documentacion, and (2) Unidad de Conductas Adictivas de Moncada, Valencia, Spain, (3) Hospital Sant Pau, Barcelona, Spain and (4) Consultant to NIDA, Atlanta, GA
Gender differences in sexual risk behaviors and seropositivity among young non-injection heroin users
R. R. Robles, T. D. Matos, H. M. Colon, J. C. Reyes, J. Calderon and J. Negron, Universidad Central del Caribe, Bayamon, Puerto Rico
Gender differences in the effect of birth cohort on risk for alcohol and drug dependence
K. Keyes and D. S. Hasin, New York State Psychiatric Institute, New York, NY
Male-female difference in risk of rapid transition to dependence among recent onset tobacco and alcohol users in Peru
M. J. Piazza(1,2) and G. F. Alvarado(1,3), (1) Universidad Peruana Cayetano Heredia, and (2) Belgian Technical Cooperation, Lima, Peru and (3) Epidemiology, Michigan State University, East Lansing, MI
Monthly patterns of smoking topography and smoking rate among college women smokers: A pilot study
G. S. Hecht(2), A. Copeland(1), D. E. Kendzor(1) and A. Finley(1), (1) Louisiana State University, and (2) Southern University, Baton Rouge, LA
What are the specific cognitive effects of transdermal nicotine and smoking, and do they depend on smoker's gender?
B. Kleykamp(1), J. M. Jennings(2), C. L. Sams(1), M. D. Blank(1), M. Weaver(1) and T. Eissenberg(1), (1) Virginia Commonwealth University, Richmond, VA and (2) Wake Forest University, Winston-Salem, NC
Gender differences in motivational and valuational processing of visual-rewarding stimuli: Implications for increased propensity to drug dependence
W. Chi(1), D. Ariely(2), N. Mazar(2), S. Dunlap(1), S. Lukas(1) and I. Elman(1), (1) McLean Hospital, Belmont, MA and (2) MIT, Cambridge, MA
Flutamide reduces benzoylecgonine levels following cocaine infusion in men
R. Yamamoto(1,2), T. L. Barros(1), E. McCarthy(2), C. Mileti(2), T. Juliano(2), A. Looby(2), M. Cote(2), J. F. McNeil(2), D. Olson(1), G. Mallya(2), S. E. Lukas(2), P. F. Renshaw(1) and M. J. Kaufman(1), (1) Brain Imaging Center, and (2) Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA
Discriminative-stimulus effects of d-amphetamine in women and men
F. Wagner(1), A. Vansickel(1), W. Stoops(1), J. Lile(1), L. Hays(2), P. Glaser(2) and C. Rush(1,2), (1) Deparment of Behavioral Science, and (2) Department of Psychiatry, University of Kentucky, Lexington, KY
Anabolic steroids: Users' and experts' perspectives
V. Agullo, S. Tortajada, M. Castellano, J. Valderrama, A. Vidal, J. Perez de Los Cobos and R. Aleixandre, Historia de la Ciencia, Universitat de Valencia, Conselleria de Sanitat, Generalitat Valenciana, and FEPAD, Valencia, Spain
Physiological, subjective and hormonal responses to acute psychological stress: Effects of sex and smoking status
E. Childs and H. de Wit, University of Chicago, Chicago, IL
Estradiol modulation of nociception, morphine antinociception, and reproductive indices in female rats
J. Sumner and R. M. Craft, Washington State University, Pullman, WA

Estradiol alters COX-1 and COX-2 activities in the lumbosacral region of the spinal cord of OVX female rats
T. Kuba, D. Hunter, S. Jenab and V. Quinones-Jenab, Hunter College, New York, NY
Estrogen's effects on inflammatory-induced pain are in part mediated through activation of cyclooxygese (COX) biosynthesis of prostaglandin E2
D. Hunter, T. Kuba, N. Amador, K. Shivers, S. Jenab and V. Quinones-Jenab, Hunter College, New York, NY
Menstrual cycle phase modulates phencyclidine (PCP) self-administration in monkeys
J. L. Newman, J. J. Thorne and M. E. Carroll, Psychiatry Research, University of Minnesota, Minneapolis, MN
Enhanced PKA-regulated signaling in female rats may contribute to sex differences in cocaine self-administration
W. J. Lynch(1), D. Kiraly(2), B. Caldarone(2), M. Picciotto(2) and J.Taylor(2), (1) University of Virginia, Charlottesville, VA and (2) Yale University, New Haven, CT

AMPHETAMINES: ANIMAL STUDIES
Methamphetamine withdrawal sensitizes the NMDA receptor resulting in excitotoxicity in the hippocampus
K. J. Smith, R. L. Self, L. Ghayoumi, M. T. Bardo and M. A. Prendergast, University of Kentucky, Lexington, KY
Dopamine mediates crosstalk between nerve endings and microglia and serves as the molecular trigger in methamphetamine neurotoxicity
D. M. Kuhn(1,2) and D. M. Thomas(1,2), (1) Wayne State University School of Medicine, and (2) John D. Dingell VA Medical Center, Detroit, MI
Prior exposure to a neurotoxic regimen of methamphetamine reveals the existence of dopaminergic neurons resistant to further effects of methamphetamine treatment
E. L. Riddle, E. Birdsall, K. S. Rau, J. L. King, J. A. Riordan, K. A. Keefe, J. W. Gibb, G. R. Hanson and A. Fleckenstein, University of Utah, Salt Lake City, UT
Effect of treatment with a selective serotonin reuptake inhibitor, paroxetine, on neurogenesis and neuroprotection
N. Kuzumaki(1), M. Narita(1), N. Hareyama(1), M. Terada(2), M. Yamazaki(2) and and (2) University of Toyama, Toyama, Japan
In vivo effects of insulin on dopaminergic function and amphetamine pharmacology
J. M. Williams(1), W. A. Owens(2), G. H. Turner(1), R. D. Blakely(1), C. P. France(2), J. C. Gore(1), L. C. Daws(2), M. J. Avison(1) and A. Galli(1), (1) Vanderbilt University Medical Center, Nashville, TN and (2) The University of Texas Health Science Center, San Antonio, TX
Streptozotocin-induced decreases in dopamine clearance and locomotion are not restored by insulin replacement
R. J. Sevak(1), W. A. Owens(2), L. C. Daws(2), A. Galli(3) and C. P. France(1), (1) Department of Pharmacology, and (2) Department of Physiology, University of Texas Health Science Center, San Antonio, TX and (3) Vanderbilt University, Nashville, TN
Environmental enrichment increases the extinction rates of amphetamine self-administration and decreases the reinstatement threshold for amphetamine-seeking behavior
D. J. Stairs and M. T. Bardo, University of Kentucky, Lexington, KY
The effects of disulfiram on methamphetamine-induced conditioned place preference
R. G. Fox(1), S. J. Stutz,(1), R. De La Garza, II(2), T. F. Newton(2), T. C. Napier(3), and K. Cunningham(1), (1) Center for Addiction Research, University of Texas Medical Branch, Galveston, TX, (2) Geffen School of Medicine at UCLA, Los Angeles, CA and (3) Loyola University School of Medicine, Maywood, IL
Discriminative-stimulus effects of adenosine antagonists in methamphetamine-trained monkeys
J. Bergman, J. Frasca, A. Zakarian and C. A. Paronis, ADARC-MRC, Harvard Medical School/McLean Hospital, Belmont, MA
Cross-substitution of nicotine and methamphetamine
M. B. Gatch, E. Flores and M. J. Forster, UNT Health Science Center, Fort Worth, TX

PHARMACOLOGICAL TREATMENTS FOR STIMULANT ABUSE
Atomoxetine for cocaine dependence
C. R. Rush(1,2), W. W. Stoops(1), F. P. Wagner(1), P. E. Glaser(2) and L. R. Hays(2), (1) Department of Behavioral Science, and (2) Department of Psychiatry, University of Kentucky, Lexington, KY
Controlled clinical trial of fluoxetine and vouchers in methadone-maintained patients with cocaine dependence
E. C. Strain(1), R. E. Johnson(1,2), K. Silverman(1) and G. E. Bigelow(1), (1) Johns Hopkins University, Baltimore, MD and (2) Reckitt and Benckiser, Richmond, VA

The effect of food on the bioavailability of RPR102681, a novel CCK-B antagonist, in normal volunteers
A. Manari(2), J. Mendelson(1,2), E. Fernandez(2), D. Harris(3) and R. T. Jones(2), (1) California Pacific Medical Center, San Francisco, CA, (2) UCSF, San Francisco, CA and (3) Department of Psychiatry, University Cincinnati and Cincinnati VA Medical Center, Cincinatti, OH

Effects of Bupropion SR on neurocognition in volunteers with methamphetamine dependence
A. D. Kalechstein, R. De La Garza, II, and T. F. Newton, David Geffen School of Medicine at UCLA, Los Angeles, CA

An open-label, dose-ranging tolerability study of N-acetylcysteine for the treatment of cocaine dependence
P. N. Mardikian(1), S. D. LaRowe(1), P. W. Kalivas(2) and R. J. Malcolm(1), (1) Center for Drug and Alcohol Programs, and (2) Addiction Research Center, Medical University of South Carolina, Charleston, SC

N-acetylcysteine and baclofen as pharmacotherapies for cue- and drug-induced cocaine craving
S.L. Amen, R.C. Risinger, L.B. Piacentine and S.J. Li, Medical College of Wisconsin, Milwaukee, WI

D-amphetamine blocks some subjective effects of intravenous cocaine in humans
C. Johanson, L. H. Lundahl and H. Schubiner, Wayne State University School of Medicine, Detroit, MI

Single-dose methamphetamine reserpine interactions
J. Mendelson(1,2), E. Fernandez(2), P. Shwoneck(2) and R. T. Jones(2), (1) California Pacific Medical Center, and (2) Drug Dependence Research, UCSF, San Francisco, CA and (3) University of Cincinnati and Cincinnati VA Medical Center, Cincinnati, OH

An open-label study of the safety and clinical effectiveness of the Prometa™ treatment protocol for methamphetamine dependence
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An evaluation of the effects of rivastigmine on neurocognition in methamphetamine-dependent volunteers
B. J. Jackson, A. D. Kalechstein, R. De La Garza, II, L. Harrison, Z. Franco and T. F. Newton, David Geffen School of Medicine at UCLA, Los Angeles, CA

Effects of rivastigmine treatment on intravenous self-administration of methamphetamine in methamphetamine-dependent volunteers
J. J. Mahoney, III, R. De La Garza, II, C. Culbertson, R. Fintzy and T. F. Newton, David Geffen School of Medicine at UCLA, Los Angeles, CA

A double-blind, placebo-controlled assessment of potential interactions between intravenous methamphetamine and rivastigmine: Cardiovascular and subjective effects
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Baseline differences in cognition between high and low use of methamphetamine in a medication trial
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Conditioned cognitive and psychomotor effects of caffeine in humans
A. Attwood, P. Terry, S. Higgs, School of Psychology, University of Birmingham, Birmingham, UK

NICOTINE: HUMAN STUDIES

An evaluation of the impact of lifetime or current smoking patterns on the acute subjective effects produced by methamphetamine in the laboratory
S. E. Evans, R. De La Garza, II, and T. F. Newton, David Geffen School of Medicine at UCLA, Los Angeles, CA

Effects of memantine and bupropion on cigarette-smoking behavior in the human laboratory
A. Bisaga, M. Scullin and M. Haney, New York State Psychiatric Institute and Columbia University, New York, NY

Effects of acute methylphenidate and atomoxetine administration on spontaneous smoking in humans
A. R. Vansickel(1,2), W. W. Stoops(2), P. E. Glaser(3) and C. R. Rush(1,2,3), (1) Department of Psychology, (2) Department of Behavioral Science, and (3) Department of Psychiatry, University of Kentucky, Lexington, KY

Randomized trial of baclofen for smoking reduction
T. R. Franklin, R. Ehrman, D. Harper, K. Kampman, K. Lynch, C. P. O'Brien and A. R. Childress, University of Pennsylvania, Philadelphia, PA

A double-blind, placebo-controlled assessment of topiramate effects on cigarette craving and reward
J. J. Palamar, S. Raghavan, P. Paunikar and M. S. Reid, New York University School of Medicine, New York, NY

Denicotinized cigarettes attenuate nicotine withdrawal symptoms, but not working memory deficits, for 8 days
S. Heishman(1), C. Myers(1), D. Lee(1), I. Berlin(2), R. Taylor(1) and E. Moolchan(1), (1) NIH/NIDA, Intramural Research Program, Baltimore, MD and (2) Groupe Hospitalier Universitaire Pitie-Salpetriere, Paris, France

Performance of Stroop tasks by smokers and non-smokers: Do cigarette smoking and withdawal affect selective attention?
C. Domier(1), J. R. Monterosso(1) and E. D. London(1,2,3), (1) Psychiatry and Biobehavioral Sciences, UCLA, (2) Molecular and Medical Pharmacology, David Geffen School of Medicine, and (3) Brain Research Institute, UCLA, Los Angeles, CA

Does cue-reactivity extinguish with repeated laboratory sessions?
M. J. Carpenter, S. LaRowe, H. Upadhyaya, M. Saladin and K. Brady, Medical University of South Carolina, Charleston, SC

Probability discounting among cigarette smokers and non-smokers: Molecular analysis discerns group differences
R. Yi, K. M. Gatchalian and W. K. Bickel, Psychiatry, University of Arkansas for Medical Sciences, Little Rock, AR

Modeling the effects of brief smoking lapses during the initial weeks of smoking cessation
L. Chivers, S. T. Higgins, R. M. White, G. J. Badger and S. H. Heil, University of Vermont, Burlington, VT

Comparison of differing components of operational definitions of relapse for smoking
K. Tracy(1), D. Donovan(2), M. Reid(1), S. Blotner(1), J. Robinson(1) and J. Rotrosen(1), (1) NIDA CTN New York Node, New York University School of Medicine, New York, NY and (2) NIDA CTN Washington Node, University of Washington, Seattle, WA

Progressive ratio responding for cigarette puffs: Effects of dieting status and cigarette deprivation in women smokers
R. A. Jenks and S. Higgs, The University of Birmingham, Birmingham, UK

What elements of MI boost change? Smoking cessation MI interventions in women post partum
C. Kufeld(1), J. Freyer(2), R. J. Thyrian(2), W. Hannover(3), K. Roske(3), G. Bischof(4), U. John(2) and U. Hapke(2), (1) Dresden U. of Technology, Dresden, (2) Institute of Epidemiology and Social Medical, and (3) Institute of Medical Psychology, University of Greifswald, Greifswald, and (4) University of Luebeck, Luebeck, Germany

Which smoking cessation intervention works for smokers with an alcohol addiction?
K. Metz(1), C. Kroeger(1), C. Schuetz(2), S. Floeter(1) and C. Donath(1), (1) IFT Institut fuer Therapieforschung, Munich, Germany and (2) Rheinische Friedrich-Wilhelms-Universitaet, Bonn, Germany

Treatment goals indicate motivation
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Early abstinence's effect on later abstinence in cigarette smokers
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In-treatment performance predicts post-treatment success in smoking cessation
R. Lamb, University of Texas Health Science Center, San Antonio, TX

How effective is smoking cessation in routine primary care in Germany? A controlled trial in 467 smokers in 167 primary care settings
E. A. Hoch, C. Schuetz, and H. U. Wittchen, Dresden University of Technology, Dresden, Germany

Predictive validity of four nicotine-dependence measures in a college sample
L. Dierker(1), E. Sledjeski(1), D. Costello(1), S. Shiffman(3), E. Donny(3) and B. Flay(2), (1) Wesleyan University, Middletown, CT, (2) Oregon State University, Corvallis, OR and (3) University of Pittsburgh, Pittsburgh, PA

Anxiety and the risk of tobacco use and tobacco dependence among adults in the United States
R. Goodwin, K. Keyes and D. Hasin, Columbia University, New York, NY

Who is smoking and who has quit: Results from the WMH surveys
C. L. Storr(1), H. Cheng(2) and J. C. Anthony(2), (1) Johns Hopkins, Baltimore, MD and (2) Michigan State, East Lansing, MI

Race differences in health service utilization associated with alcohol/tobacco use in Baltimore, Maryland
P. Clubb(2,3), F. A. Wagner(1,2,3), D. C. Browne(1,2,3) and S. Zhu(2,3), (1) DARP & School of Public Health, (2) Drug Abuse Research Program & Center for Health Disparities Solutions, and (3) Morgan-Hopkins Center for Health Disparities Solutions, Morgan State University, and Johns Hopkins University, Baltimore, MD

ALCOHOL

Contextual differences in the transition from alcohol to tobacco and illegal drug use

C. Chen(1), G. M. Tang(2), C. M. Lee(3), C. Y. Lew-Ting(4), C. K. Hsiao(2), D. R. Chen(4) and W. J. Chen(2,5), (1) National Health Research Institute, (2) College of Public Health, (3) Department of Health Education, (4) Institute of Health Policy and Management and (5) College of Medical National Taiwan University, Taipei, Taiwan

Alcohol-use problem severity among school-based youths in Mexico: The significance of distinguishing between use frequency and consequences in school-based youths

V. Rojas, B. Mancha and W. W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Alcohol-use problem severity among school-based youths in Puerto Rico: The significance of distinguishing between use frequency and consequences in populations

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Factors related to adolescent alcohol use progression

T. D. Matos, R. R. Robles, J. C. Reyes, J. Calderon, H. M. Colon and J. Negron, Universidad Central del Caribe, Bayamon, Puerto Rico

Suicidal behaviors, internalizing disorders and alcohol involvement in youth

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Differences between impaired drivers convicted in wet, moist and dry counties

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10-years' course of alcohol use and alcohol dependence from adolescence to adulthood: Findings on onset and stability from a prospective community study

A. Perkonigg(1,2), J. Rehm(1) and H. U. Wittchen(1), (1) Technical University of Dresden, *Withdrawn*

Smoking and at-risk drinking as indicators for other unhealthy behaviors

J. E. Lima(1) and E. V. Nunes(1,2), (1) New York State Psychiatric Institute, and (2) Columbia University, College of Physicians and Surgeons, New York, NY

Differences in treatment outcome between male alcohol-dependent offenders of domestic violence with and without active drug use

D. Mandel, K. M. Carroll, and C. J. Easton, Yale University, New Haven, CT

Factors associated with heavy alcohol use among women in residential drug treatment

A. A. Alvanzo, D. Svikis and D. Langhorst, Virginia Commonwealth University, Richmond, VA

Women's alcohol craving and symptoms in early recovery

C. M. Coyne, University of Washington, Seattle, WA

Self-report and behavioral measures of impulsivity in light and moderate female drinkers

S. L. Collins(1,2), E. D'Antonio(2) and S. M. Evans(1,2), (1) Columbia University College of Physicians & Surgeons, and (2) New York State Psychiatric Institute, New York, NY

Preliminary evidence of HPA axis activation and prolactin release by alcohol and opioid antagonism in humans

M. Warnecke(1), G. Koller(2), B. Bondy(2), J. Krystal(3) and C. Schuetz(1), (1) Friedrich- Wilhelms University, Bonn, Germany, (2) Ludwig-Maximilian University, Munich, Germany and (3) School of Medicine, Yale University, New Haven, CT

Individual differences in alcohol effects among high- and low-impulsive sensation seekers

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Acamprosate decreases the severity and duration of relapse and AIDS in post-relapse recovery of abstinence in alcohol-dependent patients

E. Schneider, K. Saikali, D. Zhang, A. Gage and J.Vander Zanden, Forest Laboratories, Inc., New York, NY

Responder/numbers-needed-to-treat analysis of acamprosate in alcohol dependence in the context of current CNS therapy

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Changes in functions of glutamate receptor and its modulators in the spinal cord obtained from ethanol-dependent rats with painful neuropathy

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SEDATIVE-HYPNOTICS, INHALANTS

Changes in cortical -aminobutyric-acid-ergic system under a neuropathic pain-like state in mice
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Effects of several abused solvents on seizures induced by pentylenetetrazol or N-methyl-Daspartic acid in mice
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Selective attenuation of the discriminative stimulus effects of benzodiazepines, and not other positive GABAA modulators, by pentylenetetrazole in rhesus monkeys
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Discriminative stimulus effects of flumazenil in benzodiazepine-dependent monkeys: Pharmacologic evaluation upon temporary discontinuation of treatment
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GABAA receptor subtypes and clinically relevant effects of benzodiazepines: Observable behavior and discriminative stimulus effects of L-696 in primates
S. C. Licata(1), D. M. Platt(1), G. R. Dawson(2), J. R. Atack(2) and J. K. Rowlett(1), (1) New England Primate Research Center, Harvard Medical School, Southborough, MA and (2) Neuroscience Res Centre, Merck, Sharp & Dohme Res Laboratories, Harlow, UK

Attenuation of the motor and sedative-like effects of alprazolam by flumazenil and BCCT in rhesus monkeys
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Effects of flunitrazepam (Rohypnol) on humans' risky decision-making
S. D. Lane, D. R. Cherek, O. V. Tcheremissine, L. M. Lieving and S. O. Nouvion, University of Texas Health Science Center - Houston, Houston, TX

Reducing benzodiazepine consumption in opioid maintenance therapy patients: A controlled clinical trial
O. Lopatko, K. Morefield, C. Danz, J. Davies, R. Ali and J. M. White, University of Adelaide, Adelaide, South Australia, Australia

Consumption of benzodiazepines among drug addicts in Ile de France area: Course over 5 years
S. Djezzar(1), E. Frauger(2), D. Deschamps(1), J. Micallef-Roll(2) and S. Dally(1), (1) CEIP Ile de France, Hopital Fernand Widal, Paris, and (2) CEIP PACA-Corse, centre associe, Hopital Timone, Marseille, France

Risk of sedative-hypnotic problems soon after onset of extra-medical use: United States, 2001—2003
C. F. Rios-Bedoya(1,2) and J. C. Anthony(2), (1) Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD and (2) Michigan State University, East Lansing, MI

Repeated GHB administration in rats does not affect stimulated dopamine efflux or alter autoreceptor function
G. Zhou, C. M. Kuhn and Q. D. Walker, Duke Medical Center, Durham, NC

Gamma-hydroxybutyric acid and ethanol: Comparison of behavioral, subject-rated, and observer-rated effects in subjects with histories of sedative abuse
M. W. Johnson, E. C. Strain and R. R. Griffiths, Johns Hopkins School of Medicine, Baltimore, MD

A human laboratory model of volatile solvent abuse: Preliminary results
D. J. Walker, The University of Chicago, Chicago, IL

Inhalant use-related disorders: Reliability and co-occurring drug disorders
T. Ridenour(1) and L. B. Cottler(2), (1) Pennsylvania State University, State College, PA and (2) Washington University in St. Louis, St. Louis, MO

Inhalant use in youth: What are the risks?
D. I. Lubman(1), L. Hides(1) and M. Yucel(1,2), (1) ORYGEN Research Centre and (2) Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, Victoria, Australia

HALLUCINOGENS

Hallucinogen dependence clinical features soon after onset of hallucinogen use: U.S., 2003
A. De La Torre, C. F. Rios-Bedoya and J. C. Anthony, Michigan State University, East Lansing, MI

Prevalence of chronic flashbacks in hallucinogen users: A web-based questionnaire
M.J. Baggott, E. Erowid, F. Erowid and L.C. Robertson, Helen Wills Neuroscience Institute, University of California/Berkeley, San Francisco, and Erowid, Grass Valley, CA

PCP-induced regulation of the NMDAR and development of locomotor sensitization
N.C. Anastasio and K.M. Johnson, University of Texas/Galveston, Galveston, TX

The κ-opioid hallucinogen salvinorin A produces robust neuroendocrine effects in non-human primates
E. R. Butelman, M. Mandau and M. J. Kreek, The Rockefeller University, New York, NY

Discriminative stimulus effects of DOM in rhesus monkeys

C. P. France(1), J. X. Li(1) and K. C. Rice(2), (1) University of Texas Health Science Center, San Antonio, TX and (2) NIDDK, NIH, Bethesda, MD

ADOLESCENT DRUG ABUSE II

A longitudinal study of pre-sexual risk behaviors and substance use among adolescents whose mothers are HIV positive

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The impact of HIV+ parents' drug use on their adolescent children

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Reductions in substance abuse among young people living with HIV

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Impact of a peer-mentoring program for HIV-affected youth on family functioning and mental health services participation

C. Fong(1), A. Rosenblum(1), S. Magura(1) and C. Norwood(2), (1) National Development and Research Institutes, New York, NY and (2) Health People, Bronx, NY

Institutionalization masks outcomes and biases treatment effect estimates

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Effect of motivational incentives in a community adolescent treatment center

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The impact of neighborhood disorganization and social capital on adolescent drug use, drug dependence and access to drug treatment

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Correlates of substance use among homeless youth in eight cities

S. Salomonsen-Sautel(1), C. Hopfer(1), D. Clark(1), C. Gilroy(2), S. Boyle(3) and J. M. Van Leeuwen(3), (1) Division of Substance Dependence, and (2) Division of General Internal Medicine, UCDHSC, and (3) Urban Peak, Denver, CO

Factors associated with adolescent ecstasy use in the National Survey of Parents and Youth

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Occurrence of cannabis-related problems among first-year college students

K. Caldeira(1), A. M. Arria(1), K. O'Grady(2) and E. Wish(1), (1) Center for Substance Abuse Research, and (2) Department of Psychology, University of Maryland, College Park, MD

Polysubstance use, mental health, and school dropouts in adolescent marijuana users

C. R. Duncan(1), A. Liguori(2), C. W. Mathias(1) and D. M. Dougherty(1,2), (1) Department of Psychiatry and Behavioral Medicine, and (2) Department of Physiology and Pharmacology, Wake Forest University Medical School, Winston-Salem, NC

Racial/ethnic differences in parental concern on drug use in a nationally representative sample

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Environmental indicators of AOD and violence exposure

C. D. Furr-Holden(1,2), M. Smart(1,2) and J. Pokorni(1), (1) PIRE, Calverton, MD and (2) BRIDGES for Communities, Baltimore, MD

Sexual abuse and drug involvement among middle school students in Mexico City

L. E. Ramos-Lira(1), M. A. Caballero(1), M. T. Saltijeral(1), C. Gonzalez-Forteza(1) and F. A. Wagner(2), (1) National Institute of Psychiatry, Mexico City, Mexico, D.F., Mexico and (2) DARP & School of Public Health, Morgan State University, Baltimore, MD

Chile-USA comparisons: Student drug use trends, 1995-2001

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Social markers of maturation and the transition to young adulthood in a clinical sample of adolescents treated for substance use disorders

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Predictors of substance use disorders in adolescent psychiatric inpatients

M. Weaver(1), M. Dupre(2), K. L. Cropsey(1), J. R. Koch(1), B. A. Sood(1) and J. L. Wiley(1), (1) Virginia Commonwealth University, Richmond, VA and (2) Commonwealth Center for Children and Adolescents, Staunton, VA

Prenatal substance exposures and DSM-IV disorders in adolescents

C. Larkby, L. Goldschmidt, M. Cornelius and N. Day, University of Pittsburgh, Pittsburgh, PA

An Item Response Theory analysis of DSM-IV alcohol abuse and dependence criteria in adolescents

H. L. Gelhorn(1,2), C. Hartman(1), J. Sakai(1), M. Stallings(2), S. Young(2), S. Rhee(2), R. Corley(2), J. Hewitt(2), C. Hopfer(1) and T. Crowley(1), (1) University of Colorado School of Medicine, Denver, CO and (2) University of Colorado, Boulder, CO

An Item Response Theory Analysis of DSM-IV marijuana abuse and dependence criteria in an adolescent sample

C. Hartman(1), H. Gelhorn(1), J. Sakai(1), M. Stallings(2), S. Young(2), S. Rhee(2), R. Corley(2), J. Hewitt(2), T. Crowley(1) and C. Hopfer(1), (1) University of Colorado Health Sciences Center, Denver, CO and (2) University of Colorado at Boulder, Boulder, CO

Impulsivity and age of first alcohol consumption as risk for drug and alcohol abuse in male adolescents

L. Diemen, D. Bassani, F. Pechansky, C. Szobot and F. Kessler, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

A paper-pencil abuse-neglect assessment for young adults with serious substance and conduct problems: Validity

T. J. Crowley(1), S. E. Young(2), K. M. Raymond(1) and S. K. Mikulich-Gilbertson(1), (1) University of Colorado Denver/Health Sciences Center, Denver, and (2) University of Colorado, Boulder, CO

Patterns of non-medical use of prescription stimulants in college students: Associations with ADHD and polydrug use

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Childhood ADHD and late adolescent psychosocial functioning

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Alcohol use but not cannabis use reported to contribute to depression in treatment trial of comorbid adolescents

J. R. Cornelius, D. B. Clark, O. G. Bukstein, I. M. Salloum, J. Matta and D. S. Wood, University of Pittsburgh, Pittsburgh, PA

Proximal depression symptoms, not diagnosis, predicts context of relapse among substance-abusing youth with and without comorbid depression

D. E. Ramo(1) and S. A. Brown(2), (1) SDSU/UCSD Joint Doctoral Program in Clinical Psychology, and (2) UCSD & VA San Diego Healthcare System, La Jolla, CA

Gender differences in psychiatric multimorbidity among adolescent substance users admitted to treatment

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EPIDEMIOLOGY

Suicide attempts among individuals with opioid dependence: The critical role of felt belonging

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Predictors for long-term retention in methadone maintenance treatment clinic located in 2 different countries

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Highly successful outcome with low-dose requirements in methadone maintained Hmong

G. Bart, C. Nolan and G. Carlson, Hennepin County Medical Center, and University of Minnesota, Minneapolis, MN

Substitution in routine care in Germany: Retention rates after 12 months of follow-up (COBRA)

S.M. Apelt, J. Siegert and H.U. Wittchen, Institute of Clinical Psychology and Psychotherapy, Technische Universitaet Dresden, Dresden, Saxony, Germany

Drug-related deaths in the month and year after release from English prisons between 1999 and 2001, a 48,771 cohort study

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Systemic disease among cases of fatal opioid toxicity

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Characteristics of problematic opiate users in Bordeaux (France). Rose project

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Opium and heroin dependence in Iran: One or two epidemics?

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US trends in ambulatory-care-opioid prescribing from 1993-2003
M. J. Pletcher(1), S. G. Kertesz(3), J. E. Mendelson(2) and R. Gonzales(1), (1) University of California, and (2) California Pacific Medical Center, San Francisco, CA and (3) University of Alabama, Birmingham, AL

Characterizing opioid analgesic abuse: Findings from ethnographic field research
J. P. Fitzgerald, M. Y. Smith, J. D. Haddox and A. T. Kline, Purdue Pharma LP, Stamford, CT

Male-female contrasts and other variations in exposure opportunity and actual extra-medical use of analgesics in an epidemiological study
K. Bohnert and J.C. Anthony, Michigan State University, East Lansing, MI

Low-frequency heroin injection among out-of-treatment, street-recruited IDUs
A. H. Kral(1), J. Lorvick(1), L. Gee(1), M. Iguchi(2) and L. Wenger(1), (1) RTI International, San Francisco, CA and (2) UCLA and RAND, Los Angeles, CA

Incidence and predictors of drug injection among young non-injecting heroin users in Chicago
L. J. Ouellet and D. Broz, University of Illinois at Chicago, Chicago, IL

Gender differences in older heroin users
A.H. Brown and C.E. Grella, University of California Los Angeles, Los Angeles, CA

Decreased alcohol/smoke/drug use frequency with increasing age
H. Albeck, L. Larsen and H. Nyborg, University of Aarhus, Aarhus, Denmark

Data mining FDA's post-marketing adverse-event-reports data to examine drug-dependence reporting
C. M. Dormitzer, J. M. Tonning, A. Szarfman, J. G. Levine, S. Calderon and D. B. Leiderman, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

Estimated risk of cocaine dependence soon after onset of use: United States, 2002-2003
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Changes in depressive symptomatology among young adults with a history of MDMA use
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Methamphetamine injection is independently associated with receptive needle sharing among injection drug users in Tijuana, Mexico
R. A. Pollini, K. C. Brouwer, R. Lozada, M. Firestone, C. Magis-Rodriguez, P. Case, S. Burris and S. A. Strathdee, UCSD, La Jolla, CA

Knowledge of hepatitis among rural felony probationers
C. B. Oser, C. G. Leukefeld and J. R. Havens, University of Kentucky, Lexington , KY

First-year results of the whole day first-grade program
A. M. Windham(1), J. M. Poduska(1), S. Kellam(1), C. H. Brown(1,2), C. Ford(1), J. Reid(3) and N. Keegan(1), (1) American Institutes for Research, Baltimore, MD, (2) University of South Florida, Tampa, FL and (3) OSLC, Eugene, OR

THEORETICAL/COMMENTARY

Refining an HIV risk-reduction intervention using a structural equations modeling approach
I. Lee and M. Copenhaver, University of Connecticut, Storrs, CT

Street knowledge: Using ethnography to inform and enhance street-based recruitment and retention of heroin injectors and crack smokers in HIV prevention research trials
K. T. Jones, C. Voytek, A. Fleck, J. Hammond, T. Brown, R. White, G. E. Woody and D. S. Metzger, University of Pennsylvania, Philadelphia, PA

Integration of buprenorphine into a VA narcotic treatment program in New York City: Two years later
P. P. Casadonte, Mental Health, Department of Veterans Affairs, New York Harbor Healthcare System, and New York University School of Medicine, New York, NY

Pathways to prescription opioid dependence
B. Sproule, (1) Centre for Addiction and Mental Health, and (2) University of Toronto, Toronto, Ontario, Canada

Improving signal detection in human abuse liability studies: A case for using pre-study pharmacological testing
S. L. McColl(1), K. Schoedel(1), M. K. Romach(1,2) and E. M. Sellers(1,2), (1) Ventana Clinical Research Corporation, and (2) University of Toronto, Toronto, Ontario, Canada

Prescription drug abusers: Abuse is not abuse is not abuse
S. H. Schnoll(1,2), R. Fant(1) and J. Henningfield(1,2), (1) Pinney Associates, Inc, Bethesda, (2) and The Johns Hopkins School of Medicine, Baltimore, MD and (3) Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

The Colorado Women's Prison Project: Preliminary findings at baseline - substance abuse behaviors, histories, and service needs/utilization of young and mature female offenders

M. L. Schoeneberger(1) and J. Y. Sacks(2), (1) National Development and Research Institutes-CIRP, Denver, CO and (2) NDRI-CIRP, New York, NY

Not getting research treatment: Early-screening-phase dropouts in a Modafinil trial of cocaine dependence

S. L. Hedden(1,2), R. Malcolm(2), K. Cochran(2) and K. Brady(2), (1) Department of Biostatistics, and (2) Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC

Positive psychology and addiction treatment

T. A. Steen, Charles O'Brien Center for Addiction Treatment, University of Pennsylvania, Philadelphia, PA

Development of a novel depression treatment for inner-city depressed substance users currently receiving residential substance abuse treatment

A.R. Braun, S.B. Daughters, M.N. Sargeant, E.K. Reynolds and C.W. Lejuez, University of Maryland, College Park, MD

Grooming the next generation of substance abuse clinicians: Curricular checklist to help educators infuse evidence-based practices into undergrad and graduate coursework

N. A. Roget(1), W. Woods(1) and A. H. Skinstad(2), (1) University of Nevada, Reno, Reno, NV and (2) University of Iowa, Iowa City, IA

New directions in the assessment of executive functions—commentary

A. M. Horton(1) and C. R. Reynolds(2), (1) Neuropsychology Clinic, Psych Associates of Maryland, Bethesda, MD and (2) Texas A&M University, College Station, TX

The compulsion zone model explains the dose-response curve and effect of schedules on cocaine self-administration

V. L. Tsibulsky, M. K. Norman, W. R. Buesing, M. R. Tabet and A. B. Norman, University of Cincinnati, Cincinnati, OH

The differential neuroplasticity hypotheses of drug addiction: The hypotheses and electrophysiological evidence

L. L. Peoples, University of Pennsylvania, Philadelphia, PA

A method to study pain and factors influencing pain sensitivity in aged rats

C. S. Carter(1), C. D. King(2), C. J. Vierck(2), D. Morgan(3) and R. P. Yezierski(4), (1) Institute on Aging, (2) Department of Neuroscience, (3) Department of Psychiatry, and (4) Comprehensive Center for Pain Research, University of Florida, Gainesville, FL

Challenges and outcomes in comparing smoked marijuana and oral THC

M. D. Blank, M. F. Weaver, C. L. Sams, B. A. Kleykamp, B. Martin and T. Eissenberg, Virginia Commonwealth University, Richmond, VA

Oral and dermal products elaborated with coca leaves sold over the counter. Legal implications

T. Llosa, ORAL-COCADI, Lima, Peru

Risk management and drug abuse research: Challenges and opportunities

J. E. Henningfield(1,2), R. V. Fant(1) and S. H. Schnoll(1), (1) Pinney Associates, Bethesda, and (2) Johns Hopkins School of Medicine, Baltimore, MD

Development of strategies for prevention and control of substance use problems in India: Need to focus on country specific factors

D. K. Gupta, Johns Hopkins School of Public Health, Baltimore, MD

Substance use during pregnancy in West Central Mexico

M. De La Torre-Gutierrez(1), R. Vargas-Lopez(1,3), J. A. Gutierrez-Padilla(1,3), H. Gallardo-Rincon(1), L. Avalos-Huizar(1), A. Campos-Sierra(1) and O. Campollo-Rivas(2), (1) Antiguo Hospital Civil de Guadalajara FAA, (2) Guadalajara Hospital Civil de Guadalajara, and (3) University de Guadalajara, Guadalajara, Jalisco, Mexico

Prospects for an outcomes-based performance measurement system for substance abuse treatment programs

K. M. Harris, D. F. McCaffery, G. Ridgeway and A. R. Morral, Drug Policy Research Center, RAND, Arlington, VA

Symposium VII - NEW APPROACHES FOR ADDRESSING THE CLINICAL CHALLENGES OF TREATING OPIOID-DEPENDENT PREGNANT WOMEN

Chairs: Karol Kaltenbach and Hendree Jones

Psychopharmacological management of opioid-dependent pregnant women

Peter Martin, The Psychiatric Hospital at Vanderbilt, Nashville, TN

Voucher-based incentives to reduce drug use during pregnancy

Sarah Heil, University of Vermont, Burlington, VT

Management of pain in mothers given buprenorphine: Intrapartum and post-partum strategies

Peter Selby, University of Toronto, Toronto, Ontario

When change is wanted: Transitioning from short- or long-acting opioids onto buprenorphine
Hendree Jones, Johns Hopkins Bayview Medical Center, Baltimore, MD
Discussant
Laura McNicholas, VA Medical Center, Philadelphia, PA

Oral Communications 12 -JOIN THE CLUB: AET, GHB, MDMA
Chairs: Amy K. Goodwin and Michael H. Baumann
Alpha-ethyltryptamine (AET) as a discriminative stimulus in rats
R. A. Glennon, R. Young and T. Bondareva, Virginia Commonwealth University, Richmond, VA
Interaction of MDMA and its metabolites at monoamine transporters in rat brain
M.H. Baumann(1), J.S. Partilla(1), M.A. Ayestas(1), K.M. Page(2), B.E. Blough(2) and R.B. Rothman(1), (1) NIH/NIDA/Intramural Research Program, Baltimore, MD and (2) Research Triangle Institute, Research Triangle Park, NC
Enduring structural plasticity in nucleus accumbens following MDMA (ecstasy) administration in rats
K.T. Ball, C.L. Wellman and G.V. Rebec, Indiana University, Bloomington, IN
MDMA-induced cognitive impairment in primates: Antagonism by a selective norepinephrine or serotonin, but not a dopamine transport inhibitor
B. K. Madras, M. A. Fahey, A. Fryer, L. Lynch-Moore and C. D. Verrico, NEPRC, Harvard Medical School, Southborough, MA
Clinical evaluation of MDMA-induced neurotoxicity
R. De La Torre(1,3), S. Abanades(1,4), R. Pacifici(2), K. Langohr(1), S. Pichini(2), S. Poudevida(1), M. Torrens(1,4), R. Martin-Santos(1), J. Pena Casanovas(1,4) and M. Farre(1,4), (1) IMIM, Barcelona, Spain, (2) ISS, Rome, Italy, (3) CEXS-UPF, and (4) UDIMAS-UAB, Barcelona, Spain
Does a single or low dose of ecstasy affect memory brain function?
G. Jager(1), M. Win(2), J. van Ree(1), W. van den Brink(2), R. Kahn(1) and N. Ramsey(1), (1) Rudolf Magnus Institute of Neuroscience, Utrecht, Netherlands and (2) Academic Medical Center, Amsterdam, Netherlands
A comparison of the acute behavioral effects of gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol in baboons
A. K. Goodwin(1), P. R. Brown(1), K. M. Gibson(2), E. W. Jansen(3), C. Jakobs(3) and E. M. Weerts(1), (1) Johns Hopkins University School of Medicine, Baltimore, MD, (2) University of Pittsburgh School of Medicine, Pittsburgh, PA and (3) VU University Medical Center, Amsterdam, Netherlands
Effects of GHB and triazolam on cognitive tasks in human volunteers
L. P. Carter(1), R. R. Griffiths(1,2) and M. Z. Mintzer(1), (1) Department of Psychiatry, and (2) Department of Neuroscience, Johns Hopkins University, Baltimore, MD

Oral Communications 13 - REWARDING RESEARCH ON COCAINE-INDUCED BEHAVIOR
Chairs: Jay C. Elliott and Kathleen Kantak
Repeated exposure to cocaine elicits synaptic plasticity in rat mesolimbic slice culture
T. Maeda, W. Hamabe, Y. Fukazawa, K. Kumamoto, A. Yamamoto, L. Shang and S. Kishioka, Wakayama Medical University, Wakayama, Japan
Interactions of basolateral amygdala with the dorsal prefrontal cortex and dorsal hippocampus in context-induced reinstatement of extinguished cocaine-seeking behavior
R. A. Fuchs and J. L. Eaddy, University of North Carolina, Chapel Hill, NC
Hippocampal regulation of context-induced cocaine-seeking behavior
A.L. Atkins, Y. Mashhoon and K.M. Kantak, Boston University, Boston, MA
Increases in drug-related accumbal signaling occur over time with cocaine but not sucrose self-administration
A. V. Kravitz(1), A. Simpson(2) and L. L. Peoples(1,2), (1) Department of Neuroscience, and (2) Department of Psychology, University of Pennsylvania, Philadelphia, PA
Effects of high-dose methadone maintenance on behaviors motivated by cocaine, receptive females and palatable food in male rats
E. Cummins(1), R. E. Sorge(2), D. Woehrling(2), J. Stewart(2), J. G. Pfaus(2) and F. Leri(1), (1) University of Guelph, Guelph, and (2) Concordia University, Montreal, Ontario, Canada
Reinstatement of cocaine seeking following abstinence or cocaine priming is attenuated by blockade of D1, but not NMDA, receptors in the dorsal striatum
J. C. Elliott, M. W. Feltenstein and R. E. See, Medical University of South Carolina, Charleston, SC
Blockade of CB1 receptor by AM 251 inhibits cocaine's rewarding effects and cocaine-primed relapse by a DA-independent mechanism
Z. Xi, J. Gilbert, A. Pak, X. Peng, X. Li and E. Gardner, NIDA, Baltimore, MD

Kappa opioid agonist-induced reinstatement of cocaine seeking in squirrel monkeys: A role for stress?
G. R. Valdez, D. M. Platt, J. K. Rowlett and R. D. Spealman, New England Primate Research

Oral Communications 14 - INFECTIOUS DISEASES OF ADDICTION
Chairs: Steven L. Batki and Richard S. Schottenfeld
Drug treatment response, unmet HIV treatment needs, and mortality risk of HIV+ opioid-dependent patients in a clinical trial in Malaysia
M. Mazlan(1), M. C. Chawarski(2) and R. S. Schottenfeld(2), (1) Substance Abuse Center, Muar, Malaysia and (2) Yale University, New Haven, CT
Blood sharing and gender-based violence among IDUs in Dar es Salaam, Tanzania S. A. McCurdy(1), M. L. Williams(1), G. P. Kilonzo(2), M. W. Ross(1) and M. T. Leshabari(2), (1) University of Texas Houston Health Sciences Center, Houston, TX and (2) Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania
HIV risk behavior and psychiatric symptoms among heroin addicts in Russia
E. M. Krupitsky(1), E. Zvartau(1), V. Egorova(1), M. Tsoy(1), A. Burakov(1), D. Masalov(1), E. Verbitskaya(1), T. Didenko(1), T. Romanova(1), N. Neznanov(1), A. Grinenko(1), C. O'Brien(2) and G. Woody(2), (1) St. Petersburg State Pavlov Medical University, St. Petersburg, Russian Federation and (2) University of Pennsylvania, Philadelphia, PA
HIV risk behaviors in hepatitis C- positive and negative polydrug abusers in drug treatment
K.A. Belendiuk, D.H. Epstein, J.P. Schmittner and K.L. Preston, Clinical Pharmacology and Therapeutics Research Branch, NIDA, Baltimore, MD
Prevalence and risk factors for hepatitis and HIV in substance abuse patients in West Central Mexico: Guadalajara report
O. Campollo-Rivas(1,3), G. Hernandez-Ruiz(1), A. Panduro(3), H. R. Perez-Gomez(1,3), L. Diaz-Barriga(2), M. C. Balanzario(2) and E. Aceves(2), (1) CUCS, Universidad de Guadalajara, (2) Centros de Integracion Juvenil AC, Guadalajara-Mexico, and (3) Antiguo Hospital Civil de Guadalajara, Guadalajara, Jalisco, Mexico
Quality of life in MMT patients with untreated HCV infection
S.L. Batki(1,2), K.M. Canfield(1), C. Cole, R. Ploutz-Snyder(1), J.A. Dimmock(1), H. Phamand (1) and E. Smyth(1), (1) State University of New York, Upstate Medical University, and (2) VA Center for Integrated Healthcare, Syracuse, NY
Mortality outcomes among healthy young adults who use illicit drugs (the CARDIA study)
S. Kertesz(1), M. Pletcher(2), M. Safford(1), J. Halanych(1), S. Sidney(3), J. Schumacher(1) and C. I. Kiefe(1), (1) University of Alabama, Birmingham, AL, (2) UCSF, San Francisco, and (3) Kaiser Permanente, Oakland, CA
HCV risk factors among street-recruited substance-abusing women
D. Nurutdinova, A. Ben Abdallah, S. Bradford, C. Meeks and L. Cottler, Washington University School of Medicine, St Louis, MO

Symposium VIII - METHAMPHETAMINE AND HIV: A NEW AND DANGEROUS EPIDEMIC
Chairs: Jag Khalsa and Madhavan PN Nair
Introduction
Jag Khalsa and Madhavan PN Nair, State University of New York at Buffalo, Buffalo, NY
Molecular and cellular basis of methamphetamine-induced neurodegeneration
Jean Lud Cadet, NIH/NIDA, Baltimore, MD
Methamphetamine and HIV: Medical and psychiatric complications
Antonio E. Urbina, Saint Vincent's Comprehensive HIV Center, New York, NY
Effect of methamphetamine on progression of HIV dementia
Avindra Nath, Johns Hopkins University, Baltimore, MD
Neuroimmunopathogenesis of HIV infection: Role of methamphetamine
Madhavan PN Nair, State University of New York at Buffalo, Buffalo, NY

Symposium IX - NEW APPROACHES TO DEVELOPMENT OF AGONIST THERAPIES FOR COCAINE DEPENDENCE
Chairs: S. Steven Negus and Leonard Howell
Effects of selective and mixed-action DA/5HT releasers on locomotor activity and extracellular DA/5HT levels in rat nucleus accumbens
Michael Baumann, NIDA/Intramural Research Program, Baltimore, MD

Effects of selective and mixed-action DA/5HT releasers on cocaine discrimination and cocaine self-administration in rhesus monkeys

S. Steven Negus, McLean Hospital, Havard Medical School, Belmont, MA

Effects of selective and mixed-action DA/5HT reuptake inhibitors as measured by PET imaging and behavioral studies in rhesus monkeys

Leonard Howell, Emory University, Atlanta, GA

Effects of agonist medications in cocaine-dependent human subjects

John Grabowski, University of Texas Health Science Center, Houston, TX

Discussant

David McCann, NIH/NIDA, Bethesda, MD

Oral Communications 15 - CAUGHT IN THE ACT: FUNCTIONAL BRAIN IMAGING

Chairs: Linda Porrino and Anna R. Childress

Regional brain activation patterns during acute marihuana smoking: A human fMRI study

S. E. Lukas(1,3), B. Frederick(2,3), L. Nickerson(2,3), K. Lindsey(1,3), S. Dunlap(1) and D. Penetar(1,3), (1) Behavioral Psychopharmacology Research Laboratory, (2) Brain Imaging Center, and (3) Department of Psychiatry, Harvard Medical School, Belmont, MA

Abstinence from cocaine does not modify the cerebral metabolic effects of cocaine self-administration in the prefrontal cortex of nonhuman primates

L. Porrino, T. J. Beveridge, H. R. Smith and M. A. Nader, Wake Forest University Health Sciences, Winston Salem, NC

Effects of naltrexone on [11C] raclopride binding potential and subjective high after intravenous amphetamine in humans

N. Jayaram-Lindstrom, T. Saijo, M. Inoue, A. L. Nordstrom and J. Franck, Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Limbic activation by cocaine cues presented outside awareness in cocaine patients: Prelude to craving?

A. R. Childress, Z. Wang, R. Ehrman, Y. Li, N. Sciortino, K. Marquez, J. G. Hakun and C. P. O'Brien, University of Pennsylvania School of Medicine, Philadelphia, PA

Reproducible brain activation patterns induced by the mu opioid agonist fentanyl in awake non-human primates: An fMRI study

M. J. Kaufman(1), B. Frederick(1), M. Brimson(1), S. McWilliams(2), A. Bear(2), P. F. Renshaw(1) and S. S. Negus(2), (1) Brain Imaging Center, and (2) Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, MA

Functional activity of smokers and non-smokers in a delay-discounting task

W. Bickel(1), D. Lindquist(2), J. Pitcock(1), R. Yi(1), K. Gatchalian(1), R. Landes(3) and B. Kowal(1), Department of Psychiatry, (2) Department of Radiology, and (3) Department of Biostatistics, UAMS, Little Rock, AR

Delay discounting based on activation in the ventral striatum

J. R. Monterosso(1), G. Ainslie(2) and E. London(1,3), (1) Psychiatry & Biobehavioral Sciences, UCLA, Los Angeles, CA, (2) Coatesville VA Medical Center, Coatesville, PA and (3) Molecular & Medical Pharmacology, UCLA, Los Angeles, CA

Cue-induced brain activity changes and relapse in smokers

C. G. Schutz(1), M. W. Landsberg(2), M. M. Daamen(1) and L. Scheef(2), (1) Department of Psychiatry, and (2) Department of Radiology, Wilhelm-Friedrichs-University, Bonn, NRW, Germany

Oral Communications 16 - DUAL DIAGNOSIS: THE TROUBLE IS MORE THAN DOUBLE

Chairs: Jennifer W. Tidey and Himanshu Upadhyaya

Effects of contingent incentives and bupropion on smoking in outpatients with schizophrenia

J. W. Tidey(1,2), D. J. Rohsenow(1,2), G. B. Kaplan(3) and R. M. Swift(1,2), (1) Brown University, and (2) Medical Research Service, VA Medical Center, Providence, RI and (3) Mental Health, VA Boston Healthcare System, Brockton, MA

Interactions between genotype and retrospective ADHD symptoms predict lifetime smoking risk in a community-based sample of young adults

F. J. McClernon, B. F. Fuemmeler, S. H. Kollins, M. E. Kail and A. E. Ashley-Koch, Duke University Medical Center, Durham, NC

ADHD symptom count and tobacco/other substance use among college students

H. Upadhyaya and M. Carpenter, Medical University of South Carolina, Charleston, SC

Prevalence and predictors of psychosis amongst regular methamphetamine users

R. McKetin(1), D. I. Lubman(2), J. McLaren(1), E. Kelly(1) and L. Hides(2), (1) University of New South Wales, National Drug & Alcohol Research Centre, Sydney, New South Wales, and (2) ORYGEN Research Centre, University of Melbourne, Melbourne, Victoria, Australia

Complex trauma exposure, PTSD and drug use

S. Galea(2), D. C. Ompad(1), G. Marshall(3), T. Schell(3), C. Chan(1), V. Nandi(1) and D. Vlahov(1), (1) CUES, NY Academy of Medicine, New York, NY, (2) School of Public Health, University of Michigan, Ann Arbor, MI and (3) RAND, Corp., Santa Monica, CA

The long-term influence of antisocial behavior on drug use patterns

E. E. Doherty, H. D. Chilcoat and M. E. Ensminger, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Ethnic differences in treatment for mood and anxiety disorders among individuals with comorbid substance dependence

M. Hatzenbuehler, K. Keyes and D. Hasin, New York State Psychiatric Institute, New York, NY

Addiction treatment services and co-occurring disorders: Application of an index to assess change in the dual diagnosis capability of community programs

M. P. McGovern(1), A. Matzkin(2) and J. Giard(3), (1) Department of Psychiatry, and (2) Center for Evaluative Clinical Sciences, Dartmouth Medical School, Hanover, NH; and (3) Department of Mental Health & Addiction Services, State of Connecticut, Hartford, CT

Thursday, June 22, 2006

Oral Communications 17 - OPIOIDS: MECHANISMS OF ACTION

Chairs: Bradford D. Fischer and Gary B. Kaplan

Opioid- and cannabinoid- induced antinociception in NR1 knockdown mice

B. D. Fischer and L. A. Dykstra, University of North Carolina at Chapel Hill, Chapel Hill, NC

A correlation between morphine-induced antinociception and increased CD-38 in mouse brain

L. C. Hull, T. T. Lee, L. Chen, G. Zhang, W. L. Dewey, F. L. Smith and P. Li, Virginia Commonwealth University, Richmond, VA

Opiate sensitization induces FOSB expression in cortical and limbic brain regions in C57Bl/6 mice

G. B. Kaplan(1,2), K. A. Leite-Morris(1,2), M. Klufas(1,2), V. Kerestes(1,2) and A. Stillman(1,2), (1) VA Boston Healthcare System, and (2) Boston University School of Medicine, Boston, MA

Extracellular processing of beta-endorphin in the rat striatum and cerebrospinal fluid: Evidence for the extracellular activity of insulin-degrading enzyme

B. Reed, B. T. Chait and M. J. Kreek, The Rockefeller University, New York, NY

Oral Communications 18 - WHAT'S UP WITH STIMULANTS?: MECHANISMS OF ACTION

Chairs: Eliot Gardner and Donald E. McMillan

Gamma-vinyl GABA inhibits cocaine-primed relapse by a DA-independent mechanism in rats

X. Peng(1), X. Li(1), J. Gilbert(1), A. Pak(1), C. Ashby(2), Z. Xi(1) and E. Gardner(1), (1) Behavioral Neuroscience Branch, NIDA, Baltimore, MD and (2) Saint John's University, Jamaica, NY

Preferential effects of the mGlu5 receptor antagonist, MTEP, on conditioned reinstatement of cocaine-seeking vs. primary reinforcement

R. Martin-Fardon, N. D. Stuempfig, M. A. Baptista and F. Weiss, Molecular and Integrative, Neurosciences, The Scripps Research Institute, La Jolla, CA

A mouse monoclonal antibody blocks recovery of (+)-methamphetamine self-administration in an animal model of relapse

D. E. McMillan, W. C. Hardwick, W. D. Wessinger and S. M. Owens, University of Arkansas for Medical Sciences, Little Rock, AR

Effect of aripiprazole on escalated methamphetamine self-administration in rats with an extended access

S. Wee and G. F. Koob, The Scripps Research Institute, La Jolla, CA

Symposium X - IMPROVING THE DIAGNOSIS OF DRUG USE DISORDERS: PREPARING FOR DSM-V

Chairs: Wilson M. Compton and Linda B. Cottler

Pitfalls and strengths of assessments for studying drug disorder classification

Wilson M. Compton, NIDA, Bethesda, MD

Marijuana withdrawal: An epidemiological perspective

Deborah Hasin, Columbia University, New York, NY

Are specific diagnostic criteria needed for adolescents?
Thomas Crowley, University of Colorado, Denver, CO
Epidemiological evidence for MDMA dependence
Linda B. Cottler, Washington University School of Medicine, St. Louis, MO
Discussant
Michael L. Dennis, Chestnut Health Systems, Bloomington, IL

Oral Communications 19 - TAKING CARE OF OUR KIDS: DRUGS AND ADOLESCENCE
Chairs: Catherine Stranger and Geetha Subramaniam
Development of a high school smoking-cessation program for adolescent smokers using contingency management principles
S. Krishnan-Sarin(1), A. Smith(1), D. Cavallo(1), A. McFetridge(1), T. Liss(1), T. Dahl(1), J. Cooney(2) and A. Duhig(3), (1) Yale University School of Medicine, New Haven, CT, (2) University of Connecticut, Newington, CT and (3) Indiana University-Purdue University at Indianapolis, Indianapolis, IN
Contingency management for adolescent marijuana abuse
C. Stanger(1), A. J. Budney(1) and J. L. Kamon(2), (1) Center for Addiction Research, UAMS, Little Rock, AR and (2) UVM, Burlington, VT
Feasibility of ibuprofen for cannabis dependence in adolescents
C. Thurstone(1,2) and P. D. Riggs(2), (1) Denver Health and Hospital Authority and (2) University of Colorado Health Sciences Center, Denver, CO
Modafinil and smoking behavior in adolescent and young adult smokers
C. A. Martin(1,2), T. A. Helmbrecht(1), G. Robbins(2), M. E. McKnight(2), G. E. Guenthner(1) and T. H. Kelly(1,2), (1) Department of Psychiatry, and (2) Department of Behavioral Science, University of Kentucky, Lexington, KY
Effect of tobacco craving on lapse to smoking among adolescent smokers undergoing cessation treatment
K.S. Bagot, S.J. Heishman and E.T. Moolchan, NIDA/Intramural Research Program, Baltimore, MD
Predictors of retention in an adolescent and young adult smoking-cessation trial
T. S. Schepis(1), K. A. Warren(1), C. A. Patten(2) and U. Rao(1), (1) University of Texas Southwestern Medical Center, Dallas, TX and (2) Mayo Clinic College of Medicine, Rochester, MN
Baseline depression symptoms predict post-residential substance use disorders across 1-year follow-up
G. Subramaniam(1,2), M. L. Stitzer(1), K. Kolodner(1), M. J. Fishman(1,2) and P. Clemmey(2), (1) Johns Hopkins University, and (2) Mountain Manor Treatment Center, Baltimore, MD
Victimization and substance use among adolescents entering treatment
D. C. Browne(1), P. A. Clubb(1), F. A. Browne(2) and M. L. Dennis(3), (1) Drug Abuse Research Program & School of Public Health and Policy, Morgan State University, Baltimore, MD (2) School of Public Health, University of North Carolina, Chapel Hill, NC and (3) Chestnut Hill Systems, Bloomington, IL

Oral Communications 20 - TREATING OPIATE ABUSE
Chairs: Michelle R. Lofwall and George B. O'Neil
Evaluation of the reinforcing and subjective effects of heroin in combination with dextromethorphan/quinidine
S. K. Vosburg, M. A. Sullivan and S. D. Comer, Substance Abuse, Columbia University/ New York State Psychiatric Institute, New York, NY
Withdrawal suppression efficacy of tramadol?
M. R. Lofwall(2), S. L. Walsh(2), G. E. Bigelow(1) and E. C. Strain(1), (1) Johns Hopkins University School of Medicine, Baltimore, MD and (2) University of Kentucky College of Medicine, Lexington, KY
Phase-1 evaluation of transdermal buprenorphine
R. Lanier(1), J. A. Harrison(1), E. S. Nuwayser(2), A. Umbricht(1) and G. E. Bigelow(1), (1) Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD and (2) Biotek, Inc., Woburn, MA
The Perth Naltrexone Implant Service; An overview of the first five years
G. B. O'Neil(1,2,3), G. K. Hulse(1), C. T. Chan(3) and Z. Parsons(3), (1) University of Western Australia, (2) Australian Medical Procedures Research Foundation, and (3) Go Medical Industries, Perth, Western Australia, Australia

Oral Communications 21 - LAW AND ORDER: DRUG COURT CLIENTS

Chairs: David S. Festinger and Caroline J. Easton

Neuropsychological functioning and retention of consent information in a misdemeanor drug court population
D. S. Festinger, K. Ratanadilok, N. S. Patapis, K. L. Dugosh, J. R. Croft, K. Benasutti and D. B. Marlowe, Treatment Research Institute, Philadelphia, PA

Participant factors associated with failure to complete substance abuse treatment in the Dane County Drug Court
R. Brown, University of Wisconsin School of Medicine and Public Health, Madison, WI

Baseline psychological stress predicts drug court outcomes one year later
T. F. Garrity, S. H. Prewitt, M. Joosen, M.Tindall, J. M. Webster, M. L. Hiller and C. G. Leukefeld, University of Kentucky, Lexington, KY, Erasmus University, Rotterdam, Netherlands and Temple University, Philadelphia, PA

Equal under the law: Treatment retention and outcome among cocaine-dependent patients with and without active criminal justice involvement
C. J. Easton, T. Babuscio, and K. M. Carroll, Yale University, New Haven, CT

Symposium XI - THE FRONTIERS OF INHALANT ABUSE: RECENT ADVANCES IN THE NEUROBIOLOGICAL BASIS OF VOLATILE SUBSTANCE ABUSE

Chairs: Scott Bowen and Silvia Cruz

Discriminative stimulus effects of abused inhalants
Keith Shelton, Virginia Commonwealth University, Richmond, VA

Inhalant abuse: A gateway to cocaine
Jeffery D. Steketee, University of Tennessee Health Science Center, Memphis, TN

Ligand-gated and voltage-gated ion channels as molecular targets for abused solvents
Silvia Cruz, College Granjas Coapa, Mexico D.F., Mexico

Neurophysiological mapping of toluene-sensitive cells in the rat midbrain
Edward French, University of Arizona, Tuscon, Arizona

Discussant: Recent advances in preclinical investigations of inhaled solvent abuse
Scott Bowen, Wayne State University, Detroit, MI

Oral Communications 22 -OPIOIDS: TOLERANCE AND DEPENDENCE

Chairs: Gery Schulteis and Anthony Riley

Naloxone, but not proglumide or MK-801, blocks tolerance to morphine's aversive effects
M. A. Fox(1), G. W. Stevenson(2) and A. L. Riley(3), (1) Laboratory of Clinical Science, NIMH / NIH, Bethesda, MD, (2) University of New England, Biddeford, ME and (3) American University, Washington, DC

NMDA antagonist interactions with opioids in models of tolerance and acute dependence
R. W. Morgan, R. L. Balster and K. L. Nicholson, Virginia Commonwealth University, Richmond, VA

Comparison of aversive effects of naltrexone, 6-beta-naltrexol, and nalbuphine given 4 hours after acute pretreatment with morphine
M. Evola(1), A. Deshmukh(2) and A. M. Young(1,3), (1) Texas Tech University Health Sciences Center, Lubbock, TX (2) Wayne State University, Detroit, MI and (3) Texas Tech University, Lubbock, TX

Increased anxiety-like behavior during naloxone-precipitated withdrawal from acute opioid dependence
G. Schulteis(1,2) and Z. Zhang(1,2), (1) UC San Diego School of Medicine, La Jolla, CA and (2) VA San Diego Healthcare System, San Diego, CA

Two patterns of craving induced by heroin reward and withdrawal lead to the relapse to heroin use in rats
W. Zhou and F. Zhang, Ningbo Addiction Research and Treatment Center, Ningbo, China

Withdrawal-associated increases in opiate reinforcement: Effects of candidate anti-relapse medications
S. S. Negus, McLean Hospital/Harvard Medical School, Belmont, MA

Limbic-related alterations of dopamine and opioid systems in midbrains of human heroin abusers
M. Horvath(1,2), E. Keller(2) and Y. Hurd(1), (1) Karolinska Institutet, Stockholm, Sweden and (2) Semmelweis University, Budapest, Hungary

Opioids modulate substance P expression
J. Peng(1), D. J. Zhou(1), D. S. Metzger(2), Y. Li (3) and W. Z. Ho(3), (1) Wuhan Center for Disease Prevention and Control, Wuhan, Hubei, China, (2) The Center for Studies of Addiction, U. of Pennsylvania School of Medicine, and (3) Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA

Oral Communications 23 - CONTINGENCY MANAGEMENT: EXPANDING ITS APPLICATIONS
Chairs: Kimberly Kirby and Joseph Schumacher

Differences in cocaine use among methadone maintenance patients receiving standard vs. extended periods of abstinence-based reinforcement: An interim analysis
K. C. Kirby(1,2), R. A. Corbin(1), A. K. Padovano(1), B. J. Rosenwasser(1), R. Gardner(1), M. L. Kerwin(1,3) and L. A. Benishek(1,2), (1) Treatment Research Institute, and (2) University of Pennsylvania School of Medicine, Philadelphia, PA and (3) Rowan University, Glassboro, NJ

Abstinence incentive effects in psychosocial counseling patients testing stimulant positive vs negative at treatment entry
M. L. Stitzer(1) and MIEDAR Study Team(2), (1) Johns Hopkins Medical School, and (2) CTN Mid Atlantic Node, Baltimore, MD

Delayed effects of CM behavioral day treatment compared to CM only on long-term abstinence
J. B. Milby(1), J. Schumacher(1), D. Wallace(2), S. Kertesz(1), R. E. Vuchinich(1), M. K. Gould(1), D. C. Meehan(1) and S. Sieweke(1), (1) University of Alabama at Birmingham, Birmingham, AL and (2) RHO Federal Systems Division Inc., Chapel Hill, NC

Contingency managed housing and behavioral day treatment impacts drug abstinence among homeless: Meta-analysis of five Birmingham cocaine studies
J. E. Schumacher(1), J. B. Milby(2), D. Wallace(3), R. Vuchinich(2), D. C. Meehan(2), R. Edmonds(2), S. Sieweke(2), A. H. Winslett(2) and D. Lowery(2), (1) Division of Preventive Medicine, and (2) Department of Psychology, The University of Alabama at Birmingham, Birmingham, AL and (3) Rho Federal Systems, Inc., Chapel Hill, NC

Predictors of cocaine abstinence in injection-drug-using methadone patients exposed to employment-based abstinence reinforcement
T. W. Knealing, W. Donlin, K. Kolodner, C. J. Wong and K. Silverman, Johns Hopkins University School of Medicine, Baltimore, MD

Brief cocaine abstinence induced by voucher and cash-based incentives
R. Vandrey, M. L. Stitzer and G. E. Bigelow, BPRU, Johns Hopkins University, Baltimore, MD

A motivational intervention reduces cocaine use and improves HIV medication adherence
K. S. Ingersoll(1), S. D. Ceperich(1), C. J. Heckman(2) and J. X. Cohen(3), (1) University of Virginia, Charlottesville, VA, (2) Virginia Commonwealth University, Richmond, VA and (3) University of California Santa Barbara, Santa Barbara, CA

Improved adherence to antiretroviral medication with electronic monitoring and contingency management
M. I. Rosen(1,2), K. Dieckhaus(4) and T. J. McMahon(1,3), (1) Yale University School of Medicine, New Haven, (2) VA Connecticut Healthcare System, West Haven, (3) Connecticut Mental Health Center, New Haven, and (4) University of Connecticut Health Center, Farmington, CT

Oral Communications 24 - ALCOHOL: WHAT'S THE PROOF?
Chairs: Yehuda Neumark and Conrad Wong

Alcohol use problem severity among school-based youths in the US: The significance of distinguishing between use frequency and consequences in populations
B. Mancha, V. Rojas and W. W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Ready to drink: Alcohol taste perception and young people
J. Copeland(1), P. Gates(1) and D. Stevenson(2), (1) NDARC, University of NSW, and (2) Macquarie University, Sydney, New South Wales, Australia

A multi-country study of 'non-dependent alcohol abuse: Male-female differences and other epidemiological patterns
H. Cheng and J. C. Anthony, Michigan State University, East Lansing, MI

Drinking and drug-use patterns and disorders in Israel: Results of a national household survey
Y. Neumark(1), D. Levinson(2) and A. Grinshpun(2), (1) Braun School of Public Health, Hebrew University-Hadassah, and (2) Department of Mental Health, Ministry of Health, Jerusalem, Israel

A randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of concurrent alcohol dependence and pathological gambling
T. Toneatto, B. Brands and P. Selby, Clinical Research, Centre for Addiction & Mental Health, Toronto, Ontario, Canada

A pilot trial of quetiapine for the treatment of alcohol dependence
K. M. Kampman(1), H. M. Pettinati(1), W. Macfadden(2), K. G. Lynch(1), T. Whittingham(1), C. A. Dackis(1) and K. Varillo(1), (1) University of Pennsylvania, Philadelphia, PA and (2) AstraZeneca Pharmaceuticals, Wilmington, DE

A pilot placebo-controlled trial of memantine for alcohol dependence

S. M. Evans(1,2), F. R. Levin(1,2), D. J. Brooks(2) and F. Garawi(2), (1) Columbia University College of Physicians & Surgeons, and (2) New York State Psychiatric Institute, New York, NY

Relationships between emergency room utilization and measures of alcohol use based on an intensive schedule of random breath sample collections and self-reports in homeless alcoholics

C. J. Wong, K. Broadwater, P. Nuzzo, M. Needham, M. Fingerhood, G. Bigelow, D. Svikis and K. Silverman, Johns Hopkins University, Baltimore, MD

Brunch with Champions

Symposium XII - ADDRESSING PRESCRIPTION OPIOID ABUSE IN THE 21st CENTURY

Chairs: Charles Grudzinskas and Robert Colucci

Lessons from the past that may assist the development of current and future opioid analgesics

Donald Jasinski, Johns Hopkins Bayview Medical Center, Baltimore, MD

The role of abuse liability studies in evaluating prescription opioid abuse

Sandra D. Comer, College of Physicians and Surgeons of Columbia University, New York, NY

Opportunities for evaluating abuse liability during clinical development and post-marketing

Nathaniel Katz, Inflexxion, Inc., Newton, MA

Oral Communications 25 - TO SLEEP OR NOT TO SLEEP

Chairs: Scott Lukas and Richard Foltin

Sleep problems in treatment-seeking opiate-dependent individuals

C. K. Burke, J. M. Pierce, D. Neubauer, N. Punjabi, K. Stoller, K. Neufeld and R. K. Brooner, School of Medicine, Johns Hopkins University, Baltimore, MD

Sleep homeostasis in methadone-maintained versus control subjects

G. H. Trksak(1,4), C. Dorsey(2,4), J. E. Jensen(3,4), W. L. Tartarini(2), T. Juliano(2), Z. Su(1), B. Cuadra(2), M. J. Kaufman(3,4), P. F. Renshaw(3,4) and S. E. Lukas(1,4), (1) BPRL, (2) Sleep Research Program (3) Brain Imaging Center, and (4) Harvard Medical School, Belmont, MA

Bupropion reduces some of the symptoms of marihuana withdrawal in chronic marihuana users

D. Penetar, A. Looby, E. Ryan, M. Cote and S. Lukas, Behavioral Psychopharmacology Research Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Effects of smoked marijuana on sleep during simulated shift work

S. Shakibaie, C. L. Hart and R. W. Foltin, Columbia University, New York, NY

Oral Communications 26 - EPIDEMIOLOGY COUNTS!

Chairs: Mary-Lynn Brecht and William W. Latimer

Rates of HIV, hepatitis A, and hepatitis C among African-American and White drug users

R. Griffin, A. Melnikov, D. Alama, D. K. Gupta, P. Chatterjee and W. W. Latimer, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Mortality and cause of death over 25 years among opiate users: Comparisons by gender and ethnicity

M. Brecht and C.E. Grella, Integrated Substance Abuse Programs, University of California at Los Angeles, Los Angeles, CA

Drug-related death cases in Budapest, Hungary between 1999-2005

E. Keller(1), E. Ujhelyi(2) and M. Horvath(1), (1) Semmelweis University, and (2) St. Laszlo Hospital, Budapest, Hungary

Description of IDUs in an HIV pre-epidemic setting

M. M. Eisenberg(1), E. Lawental(2), M. Schori(2), M. Blank(1), D. Metzger(1) and G. Woody(1), (1) University of Pennsylvania, Philadelphia, PA and (2) HDATC, Haifa, Israel

Convergence of HIV seroprevalence among injecting and non-injecting drug users in New York City: A new stage in a very large HIV epidemic

D. C. Des Jarlais, K. Arasteh, T. Perlis, H. Hagan, A. Abdul-Quader, D. Heckathorn, C. McKnight, H. Bramson, C. Nemeth, L. Torian S. Friedman, Beth Israel Medical Center, NYC Dept. of Health and Mental Hygiene, NY, Centers for Disease Control and Prevention, Atlanta, GA, NYS Dept. of Health, NY and Cornell University, Ithaca, NY

A comparison of medical service utilization patterns between hospital and community-based syringe-exchange program attendees

C. L. Masson(1), J. L. Sorensen(1), D. C. Perlman(2), M. S. Shopshire(1), K. A. Sporer(1), D. C. Des Jarlais(2) and S. M. Hall(1), (1) University of California at San Francisco, CA and (2) Beth Israel Medical Center, New York, NY

Trajectories of heroin addiction: Growth mixture modeling results based on a 33-year follow-up study
Y. Hser(1), D. Huang(1), C. Chou(2) and M. Anglin(1), (1) UCLA Integrated Substance Abuse Programs, and (2) USC Preventive Medicine, Los Angeles, CA

Injection drug-user characteristics from three Ukraine cities
R.E. Booth(1), J.T. Brewster(1), S. Dvoryak(2) and L. Sinitsyna(3), (1) University of Colorado Denver Health Sciences Center, Denver, CO, (2) Ukrainian Institute on Public Health Policy, and (3) Counterpart International, Kiev, Ukraine

Oral Communications 27 - SEX MATTERS
Chairs: Joshua Lile and Nancy Mello

Cocaine alters hippocampal and striatal progesterone and alloprogesterone levels in both male and female rats
V. Quinones-Jenab(1), A. C. Minerly(1), A. Akahvan(1), K. Weierstall(1), S. Jenab(1) and C. A. Frye(2), (1) Hunter College, New York, NY and (2) The University at Albany, State University of New York, Albany, NY

Gender differences in cocaine withdrawal-associated 5-HT 2A serotonin receptor signaling in amygdala
G. A. Carrasco(1), W. A. Wolf(2,3) and G. Battaglia(1), (1) Loyola University Chicago, Maywood, IL, (2) Research Services, Hines VA, Hines, IL and (3) University of Illinois at Chicago, Chicago, IL

Estrous cycle and hormonal influences on cocaine-primed reinstatement of drug seeking in female rats
M. W. Feltenstein, R. H. Mehta and R. E. See, Medical University of South Carolina, Charleston, SC

Progesterone blocks acquisition and expression of cocaine reward through blocking spatial memory formation
W. Sun(1,2), S. Russo(1,2), A. C. Minerly(1,2), K. Weierstall(1,2), A. Nazarian(1,2), E. Festa(1,2), T. Niyomchai(1,2), A. Akahavan(1), V. Luine(1,2), S. Jenab(1,2) and V. Quinones-Jenab(1,2), (1) Hunter College, and (2) Graduate Center of CUNY

Interactions of gender and menstrual cycle phase with progressive ratio measures of cocaine self-administration in cynomolgus monkeys
N. K. Mello, I. M. Knudson and J. H. Mendelson, Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA

Estradiol enhances the discriminative-stimulus and self-reported effects of d-amphetamine in healthy pre-menopausal women
J. A. Lile, S. L. Kendall, S. Babalonis, C. A. Martin and T. H. Kelly, University of Kentucky, Lexington, KY

Toward a better understanding of the relationship between gender and crack/cocaine use
E. K. Reynolds(1), M. A. Bornovalova(1), S. B. Daughters(1), J. J. Curtin(2) and C. W. Lejuez(1), (1) University of Maryland, College Park, MD and (2) University of Wisconsin, Madison, WI

Gender differences in patterns of adolescent smoking: Potential effects of social environment
E. Luther, M. Jaszyna-Gasior, K. S. Bagot, E. Thorner, M. B. Royo, M. Leff and E. T. Moolchan, National Institute on Drug Abuse, Baltimore, MD

Symposium XIII - EXCITED TO GET TOGETHER: GLUTAMATE ASSOCIATED SCAFFOLDING PROTEINS IN STIMULANT-INDUCED PLASTICITY
Chair: Karen K. Szumlinski

Constitutive Homer proteins: Critical regulators of stimulant sensitivity
Karen K. Szumlinski, University of California, Santa Barbara, CA

Glutamate-dopamine interplay in the postsynaptic density: Role of PSD-95 and implications in psychostimulant action
Wei-Dong Yao, Harvard Medical School, New England Primate Research Center, Southborough, MA

Cdk5 signaling pathways
James A. Bibb, University of Texas Southwestern Medical Center, Dallas, TX

Oral Communications 28 - SEDATIVE/HYPNOTICS: KNOCK YOURSELF OUT!
Chairs: James Rowlett and Scott Bowen

Toluene produces antidepressant-like effects in the forced swimming test
S. L. Cruz, P. Soberanes, D. P. Ponce and C. Lopez-Rubalcava, Farmacobiologia, Cinvestav, Mexico, Distrito Federal, Mexico

Changes in locomotor activity and toluene blood concentrations following repeated binge toluene exposures in adolescent rats
S. Bowen, J. Batis and J. Hannigan, Wayne State University, Detroit, MI

Characterization of L-891,190, a novel GABAergic compound
S. J. Kohut and N. A. Ator, Johns Hopkins School of Medicine, Baltimore, MD

GABAA receptor subtypes and clinically relevant effects of benzodiazepines: Anti-conflict and reinforcing effects of L-696 in primates

J. K. Rowlett(1), D. M. Platt(1), G. R. Dawson(2) and J. R. Atack(2), (1) New England Primate Research Center, Harvard Medical School, Southborough, MA and (2) Neuroscience Research Centre, Merck, Sharp & Dohme Research Laboratories, Harlow, UK

NIDA DIRECTOR'S REPORT TO CPDD MEETING: PROGRESS, CHALLENGES AND OPPORTUNITIES IN THE FIELD OF ADDICTION

Nora D. Volkow, Director

National Institute on Drug Abuse, Bethesda, MD

Scientific research has given us an understanding of drug addiction as a disease of the brain; unfortunately this knowledge has not been sufficient for the most part to modify the attitudes regarding policies towards and treatment of the drug addicted person. Historically, the prevailing attitudes have tended to dismiss substance abuse and addiction as manifestations of character flaws; their consequences, self-inflicted. This belief, which fostered a stigmatizing and predominantly punitive culture, lifted the responsibility of addressing the root causes of addiction off of society's shoulders, placing it squarely upon individuals whose cognitive systems and underlying brain processes, we now know, are seriously impaired. The difficulty to remove the stigma is in part due to the belief that as humans we are fully responsible and in control of our emotions, desires and behaviors. While this may be true for healthy subjects science is starting to document how repeated drug administration can disrupt the neurobiological processes responsible, among others, for free will and self-control. These changes are being described at the cellular and circuit level and can directly interfere with responses of an individual shifting a voluntary behavior to a reflexive and automated one. We are also starting to understand how genes, critical life stages and our physical and social environment, starting during fetal development and continuing through childhood, adolescence and adulthood, can modify the risk for experimenting with drugs and for becoming addicted. This paper summarizes the priorities and opportunities in drug abuse and addiction research within the current budget constraints of the National Institute on Drug Abuse.

BUDGETARY ENVIRONMENT: A FOCUSING FORCE

It is instructive to begin by contrasting the scope of the problem with the resources we have at our disposal to address it. It has been estimated that alcohol, nicotine, and other substance abuse disorders (SUDs) may cost Americans upwards of half a trillion dollars a year (ONDCP, 2004, Morbidity and Mortality Weekly Report, 2005 and Harwood, 2000) in combined expenses and lost revenue. Predictably, the key components in this figure have been increasing steadily, in real dollars, over recent years (ONDCP 2004). In contrast, NIDA's budget, which represents roughly 0.2% of this estimated cost, has been declining in real dollars for the past three appropriation cycles. We choose to cast a positive light on this reality, by viewing the monetary constraint as an opportunity to focus our efforts on projects and programs that address the truly central issues. The economic outlook, combined with our current knowledge of addiction, has helped NIDA chart a rational path into the future that concentrates our research efforts into three identifiable priority areas: prevention, treatment and HIV/AIDS.

PREVENTION RESEARCH: APPLYING THE LESSONS OF A MULTIDISCIPLINARY BOTTOM-UP APPROACH

The overriding goal of our prevention efforts is to prevent the onset of drug use and the escalation to addiction in those who have already initiated use, realizing that, by preventing drug abuse, we are also preventing the myriad adverse health, social, and economic consequences of addiction. In order to achieve these goals we pursue a multi-pronged, bottom-up strategy designed to better understand the underlying factors (e.g., genetic, developmental, environmental, comorbidities) that contribute to abuse and addiction. A better description of the mechanisms underlying abuse and addiction will allow for the rational development of interventions that are solidly grounded on scientific evidence rather than "common sense" assumptions.

We now have much more powerful tools to identify the genetic variations associated with a higher or lower vulnerability for addiction. We recognize that vulnerability to addiction is likely to reflect the contribution of multiple interacting genes and that such contributions may modulate the risk for addiction either indirectly (e.g., by affecting temperament, level of risk aversion) or directly (e.g., by affecting the pharmacological response to a given drug and the plastic changes that result in conditioned responses and compulsive drug use). Wide-genome association studies of addiction are now being undertaken, which expand our ability to assess the potential contribution of multiple genes to addictions. Indeed, results from convergent studies point to many allelic variants

that are likely to provide the heritable components of human addiction vulnerability (Uhl 2006), among which are not only the expected genes (DAD2 receptors, GABA-A receptors, nicotine receptors, μ opiate receptors) but also genes that modulate synaptic function and linked to the molecular changes associated with learning.

Carrying it a step further in the ladder of complexity, we are beginning to develop a scientific framework to codify and understand the contribution of environmental (e.g., social milieu, stress, peer pressure) and developmental (e.g., prenatal, pre-adolescent exposure) factors and how these in turn interact with genetics (i.e., genes x environment x development interactions). Naturally, our goal is to eventually understand how the interactions among all these variables impact the overall risk of addiction. This approach has already led to findings with profound clinical and social implications. Consider, for example, that the period of adolescence is characterized by both increased risk for drug experimentation and drug addiction and dramatic plastic changes in the brain (Toga *et al.* 2006). Such observations make it imperative that we investigate the impact of psychoactive drug exposure on dynamically maturing brain systems, and how this interaction influences both vulnerability to and the long term consequences of drug abuse. We have come to recognize too that some of the developmental, genetic and environmental factors linked with drug experimentation and addiction are not specific to, but are associated with greater risks for other behavioral disorders. In the case of genetics for example, studies have found associations of genes with externalizing disorders, one of which is substance abuse. Similarly, the developmental trajectories of the brain are likely to be linked with increased risks in certain individuals for clusters of behaviors such as drug experimentation, gang participation and reckless driving. Finally, social stressful environments are associated with a greater vulnerability not just for drug abuse, but also for other disorders including depression and obesity. Therefore, the challenge before us is to understand how these vulnerabilities affect the neurobiology of the brain resulting in behavioral dysfunction. The unique relevance of the genetic developmental interaction in brain function and its potential relevance for drug abuse is highlighted by the recently made connections between allelic variations in the X-linked monoamine oxidase A (MAO-A) gene, and their differential impact upon the morphology and function of the anterior cingulate gyrus (ACG) and the amygdala, which are two key regions implicated in emotion regulation and cognitive control, and in the generation of emotions respectively (Meyer-Lindenberg *et al.* 2006). Inasmuch as the allelic variations in the MAO-A gene have not been associated with differences in MAO-A activity in the adult brain (Fowler *et al.* in press) this suggests that the effects of variations in the MAO-A gene are exerted early during developmental stages. Reduced ACG activity and enhanced reactivity of the amygdala could explain at least part of the previously reported association between MAO-A and impulsive aggression. This finding is also of interest to drug abuse researchers, because they suggest that the long known effects of tobacco smoking on reducing MAO activity may have enduring behavioral consequences if prenatal exposure to cigarettes can indeed alter brain development in this fashion. Moreover, it is also likely that prenatal cigarette smoking would be more deleterious in those infants with the MAO-A allele gene that leads to lower enzyme concentration, in whom the added insult from maternal smoke-induced decreases in MAO activity, would result in even lower levels of MAO in brain. Since low or absent levels of MAO in brain during development are linked with aggressive phenotypes, this could exemplify a development x environment x gene interaction effect on the risk for a range of behaviors that could include conduct disorders and substance abuse.

NIDA recently issued two initiatives to encourage new research in such critically important and complex areas. Our 2005 Social Neurosciences RFA exemplifies our commitment to understanding the complex network of bi-directional influences that flow between the neural circuits of the brain and the social context in which they operate. The same year, NIDA released its Epigenetics of Neurobiology and Addiction RFA, an initiative that aims to develop the technologies that will facilitate epigenetic research in neurosciences (i.e., neuroplasticity), including those needed to investigate the relationship between genes, neurobiology and behavior.

TREATMENT INTERVENTIONS

Our research must ultimately result in the generation of effective ways to facilitate abstinence and prevent relapse in drug abusers. Recent advances in brain imaging, neurochemistry and molecular biology have added critical depth to our understanding of the complex etiology and pathophysiology of addiction, revealing, along the way, new molecules and structures that could be targeted by newly developed pharmaceutical, behavioral and/or combined drug addiction therapies. In this context, we've come to recognize that drug-induced changes can be long-lasting and impact a broad array of interconnected brain circuits. The collective findings in this regards strongly suggest that an effective treatment will have to not only counter the acute effects of abused drugs on the brain, but also a)

restore the value of natural rewards; b) reinstate control over impulses and behaviors; c) restore cognitive function, d) interfere with conditioned responses and e) counteract stress responses.

We have exciting products in the research & development pipeline. An immunological strategy is being evaluated to address relapse related to re-exposure to the drug. The basic idea of this approach is to induce the production of antibodies that can sequester the drug while it is still in the periphery, preventing it from ever reaching the brain and/or modifying its pharmacokinetics. Active immunization with drug-protein conjugate vaccines has been tested for cocaine, heroin, methamphetamine, and nicotine in animals. Moreover, in preliminary clinical trials a cocaine vaccine produced a robust and dose-related increase in anti-cocaine antibodies (Kosten *et al.* 2002); and in a 12-week out-patient trial, patients given a larger dose had significantly more cocaine-free urines than those given a smaller dose of vaccine (95 versus 55% cocaine-free urines) (Martell *et al.* 2005). Should such a vaccine prove effective in preventing relapse, then additional studies will be needed to optimize treatment regimens and determine what populations can be safely and effectively treated with this approach.

Also worth-highlighting is a particularly promising new pharmacotherapeutic approach that takes advantage of the recent characterization of heterodimeric neurotransmitter receptors in the brain with entirely novel biological properties. Receptors—cell surface proteins that recognize, bind, and transmit the effects of specific messenger molecules—often work in pairs (i.e., dimers). These receptor combinations, especially those with dissimilar (i.e., heterodimer) members, can generate a broader range of neuronal responses. Targeting receptor dimers as opposed to separate receptors offers new opportunities for designing highly selective *bivalent* compounds able to bind to multiple receptors and dramatically expand medication options. The compound MDAN-21, for example, represents such an exciting new development, for it engages heterodimeric opiate receptors (μ agonist and δ antagonist) with a powerful analgesic action without producing tolerance and physical dependence (Daniels *et al.* 2005).

And, in an exciting development, scientists have used real-time functional brain imaging to train healthy volunteers and chronic pain patients to control their perception of pain. In the study, participants were able to "somehow" regulate a brain region involved in pain processing (ACG) by observing its activity on real-time brain imaging scans. The mechanisms involved in this "biofeedback" process offers new possibilities for patients to regulate their emotions (deCharms *et al.* 2005). Naturally, it is critical to evaluate whether or not these effects persist and have the potential for a long-term therapeutic benefit, so important in craving control and relapse prevention. If so, the strategy could perhaps one day enable patients to voluntarily control the disordered thinking that underlies addictions and other compulsive behaviors.

HIV/AIDS AND DRUG ABUSE

A significant portion of NIDA's treatment portfolio incorporates the need to respond to the ongoing epidemic of HIV/AIDS, under the motto "drug abuse treatment *is* HIV prevention". Our multifaceted HIV related research is designed to learn as much as possible about the pivotal role of drug abuse in the spread of HIV/AIDS and to develop effective strategies to prevent and treat this disease. The diagnostic and treatment gap is one of the areas that deserved a heightened attention. Roughly 280,000 Americans are unaware of their human immunodeficiency virus (HIV) infection. Yet, recently published economic models show that in most cases routine, voluntary screening for HIV, once every three to five years, would be justified on both clinical and cost-effectiveness grounds (Paltiel *et al.* 2005). Almost thirty years after the first cases of AIDS were reported, there appear to be significant and largely untapped prevention opportunities. NIDA is eager to further explore the possibility that routine HIV screening in health care settings, including substance abuse treatment programs in the criminal justice system and in the wider community, is a public health intervention that should be expanded (Paltiel *et al.* 2005).

BLENDING SCIENCE AND PRACTICE: TRANSLATING THE SCIENCE INTO THE COMMUNITY

Maximizing the value of science requires that we emphasize the importance of having efficient systems that help implement and translate scientific findings into clinical practice. Two of NIDA's flagship programs in this regard are the National Drug Abuse Clinical Trials network (CTN) and the NIDA Criminal Justice Drug Abuse Treatment Studies (CJ-DATS).

With the CTN, NIDA has launched an efficient platform from which treatment researchers and community-based service providers can cooperatively develop, validate, refine, and deliver new treatment options to patients in

community-level clinical practice. This unique partnership between community treatment providers and academic research leaders is ideally suited to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations, and to ensure the timely transfer of research results to physicians, clinicians, providers, and patients. On the other hand CJ-DATS was born out of a pressing need to understand how to provide better drug treatment services for criminal offenders to alter their drug use and criminal behavior. CJ-DATS is a cooperative research program that explores the issues related to the complex system of offender treatment services. Nine research centers and a Coordinating Center were created in partnership with researchers, criminal justice professionals, and drug abuse treatment practitioners to form a national research infrastructure. This program, which represents an outstanding example of cooperation between Federal agencies and the research community, has already produced exciting data that gives reason for hope. Tantalizing new results do indeed suggest that a treatment-oriented approach can contribute significantly to our efforts to help many in the criminal justice population brake free from the cycle of addiction and recidivism (Kinlock *et al.* 2005).

EMERGING AND CONTINUING CHALLENGES

NIDA's ongoing strategic initiatives are the product of a careful matching of current public health needs, past accomplishments and growing research capabilities. The resulting portfolio reflects a comprehensive approach to addressing the persistent and costly problem of drug abuse and addiction in this country and the rest of the world, but it would be incomplete if it were to lack the programmatic flexibility needed to tackle harmful new trends that bubble up frequently, albeit unpredictably. Presently, one of the most worrying examples of an emerging drug-related problem is the non-medical use or abuse of prescription drugs in this country. Prescription drug abuse is certainly not a new problem, but recent prevalence estimates evince truly dangerous trends (SAMHSA 2004). Most people take prescription medications responsibly; however, an estimated 48 million people (ages 12 and older) have used prescription drugs for non-medical reasons in their lifetimes. This represents approximately 20 percent of the U.S. population. Furthermore, according to NIDA's 2006 *Monitoring the Future* study, 9.7 percent of high school seniors used hydrocodone (Vicodin) in the past year (Johnston *et al.* 2006). And the elderly are also among those most vulnerable to prescription drug abuse or misuse because they are prescribed more medications than their younger counterparts. NIDA hopes to reduce the scope of this problem by increasing awareness and supporting new research on prescription drug abuse. To this end NIDA, has issued an RFA that encourages research on the intersection of the use of opioids in the treatment of pain and the abuse and addiction to opioids. Because of the multifaceted nature of the issue, this RFA is designed to support a broad range of research ventures including epidemiology, neuroscience, developmental, prevention and treatment (behavioral, pharmacological and services approaches) research, and will support both animal and human studies.

A VISION FOR THE FUTURE

Even as we work to meet continuing and emerging challenges, we recognize the importance of investing on innovation and to contribute to the wider NIH community's effort to expand the boundaries of the scientific enterprise. Our research portfolio may be comprehensive but in this age of unprecedented scientific possibility, it is essential to look out for and be ready to take advantage of scientific opportunities as they arise. To this end NIDA has partnered with other institutes and is committed to the success of the NIH Roadmap for Medical Research Initiative. The "Roadmap" is a multi-Institute endeavor put in place to increase synergy across the NIH, to identify roadblocks in the way of progress, and to nurture creative ideas with the potential to transform the scientific enterprise. NIDA's contribution to Roadmap initiatives has steadily increased since the program's inception, from an initial investment of $3.4M to an expected level of $12M by FY07. For the past two years, fifteen Roadmap grants have been awarded to NIDA researchers. The experimental space provided by NIH Roadmap efforts complements beautifully with NIDA's vision for a balanced and effective use of research dollars.

We hope that this NIDA's multi-pronged approach will help reduce the devastating medical and social consequences of drug addiction.

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LIST OF EDDY AWARD RECIPIENTS

2006	Ivy Carroll
2005	Conan Kornetsky
2004	James H. Woods
2003	Charles P. O'Brien
2002	Horace H. Loh
2001	Kenner C. Rice
2000	William L. Dewey
1999	Mary Jeanne Kreek
1998	John W. Lewis
1997	Martin W. Adler
1996	Griffith Edwards
1995	Herbert D. Kleber
1994	Jerome H. Jaffe
1993	Lee N. Robins
1992	Joseph V. Brady
1991	Phillip S. Portoghese and Akira E. Takemori
1990	Charles Schuster
1989	Leo E. Hollister
1988	Albert Herz
1987	Clifton K. Himmelsbach
1986	Harold Kalant
1985	Louis S. Harris
1984	Raymond Houde
1983	Eric Simon
1982	Vincent Dole and Marie Nyswander
1981	Everette L. May
1980	Avram Goldstein
1979	E. Leong Way
1978	Hans Kosterlitz
1977	William Martin
1976	Abraham Wikler
1975	Harris Isbell
1974	Maurice Seevers

INTRODUCTION OF THE NATHAN B. EDDY RECIPIENT

Michael Kuhar

Emory University

I take great pleasure in introducing Ivy Carroll as the 2006 recipient of the Nathan B. Eddy Memorial Award. I have known Ivy for almost 20 years and have been impressed by his many contributions to the drug abuse research field.

Ivy received a B.S. degree in chemistry from Auburn University in 1957 and a Ph.D. in organic chemistry from the University of North Carolina at Chapel Hill in 1961 under the guidance of Dr. Richard G. Hiskey. Upon completion of his Ph.D., Ivy joined the Research Triangle Institute as a chemist, where he worked with the late Dr. Monroe E. Wall on the design, synthesis, and development of anticancer drugs. He was promoted to Senior Chemist in 1964, Group Leader in 1968, Assistant Director in 1971, and Director of Organic and Medicinal Chemistry in 1975. During this time frame, Ivy initiated his own research programs involving the design, synthesis, and evaluation of potential drugs to treat drug addiction. Ivy served as Research Vice President of the Chemistry and Life Sciences Unit from 1996–2001 and also retained his position as Director of Organic and Medicinal Chemistry, a position he still holds. In 2003, Ivy was selected as the first RTI Distinguished Fellow. At present, Ivy is Director of Organic and Medicinal Chemistry and Distinguished Fellow for Medicinal Chemistry (a position equivalent to Vice President) at the Research Triangle Institute.

During his career, Ivy's research efforts have been largely focused on drug design and discovery. He has made significant contributions in anticancer, antiradiation, antimalarial, and drug abuse research areas. Ivy has authored 373 publications, 30 book chapters, and 32 patents in the process of conducting these studies. During the course of his studies, Ivy has trained 90 postdoctoral fellows. He presently has NIH (NIDA) grants to support his efforts to develop new pharmacotherapies to treat patients addicted to cocaine, methamphetamine, heroin, and smoking.

Ivy's early studies led to the development of [^{125}I]RTI-55, [^{125}I]RTI-121, [^{125}I]RTI-229, and [^{125}I]RTI-EINT for use in studying monoamine transporters. [^{125}I]RTI-55 and [^{125}I]RTI-121 are both marketed by Perkin Elmer and are used by many scientists in their own research. Both RTI-55 and RTI-121 have been labeled with iodine-123 and carbon-11, and they have been used in Single Photon Computed Tomography (SPECT) and Positron Imaging Tomography (PET) imaging studies in rats and baboons. These studies led to the development of [^{123}I]RTI-55 (Dopascan) as a diagnostic agent for Parkinson's Disease. Thousands of patients have been diagnosed.

In other studies Ivy's research led to the synthesis of over 700 3-phenyltropane analogs of cocaine for use in a structure activity relationship (SAR) study. Highly potent and selective compounds for the cocaine-binding site on the dopamine, serotonin, and norepinephrine transporters resulted. Rat and monkey behavioral studies suggested that several of these compounds had high potential as pharmacotherapies for treating cocaine abuse. One of these compounds RTI-336 is in advanced preclinical development for treating cocaine addiction.

Ivy has also conducted research directed toward opioid and nicotinic receptors. Those studies led to the selective kappa opioid receptor antagonist JDTic, which is in preclinical development for treating cocaine relapse. His nicotine research has led to a number of agonists, partial agonists, and antagonists for nicotinic acetylcholine receptors. One of the more important is the epibatidine analog 4-nitro-PFEB, which is the most potent and selective $\alpha4\beta2$ nAChR antagonist presently available.

For many years, Ivy has been an active participant at CPDD meetings, has been a regular member of the CPDD since 1993, and recently has been elected a CPDD Fellow. He served on the Board of Directors, the Nominating Committee, Long-Range Planning Committee, and the DEC Liaison Committee as Chairman for two years. He has served on several NIH NIDA review committees, most recently the NIH Molecular Neuropharmacology and Signaling Study Section.

Ivy has been very active in other professional societies. He is a member of the American Chemical Society, the American Association for the Advancement of Science, the American Association of Pharmaceutical Scientists, and the honor societies, Sigma Xi, and Phi Lambda Upsilon. His other professional and scientific activities include

service on the Long-Range Planning Committee of the Medicinal Chemistry Section of the American Chemical Society and two terms of service on the ACS Offices and Awards Committee. He was Chairman for the last term. Ivy served on the Editorial Advisory Board of the Journal of Medicinal Chemistry from 1995 to 1999 and is presently the Medicinal Chemistry Section Editor for *Drug Development Research* and is on the advisory boards of several other organic and medicinal chemistry journals.

His awards and honors that recognize his research accomplishments include the 2002 American Chemical Society Medicinal Chemistry Award, the RTI 2001 Margaret E. Knox Excellence Award, the 2001 Herty Award, the 2000 Southern Chemist Award, and the 1993 Distinguished Lecturer Award from the North Carolina Section of the American Chemical Society. In addition, Ivy was honored by the National Institute on Drug Abuse with the 1993 Pacesetter Award and the 1996 MERIT Award for his research on the biochemical mechanisms of the action of cocaine.

2006 NATHAN B. EDDY MEMORIAL AWARD LECTURE

Design and Development of Pharmacotherapies for Substance Abuse

F. Ivy Carroll

Center for Organic and Medicinal Chemistry, RTI International, Research Triangle Park, NC

It goes without saying that I am highly honored to be the 2006 recipient of the Nathan B. Eddy Memorial Award. Even though I have received a number of awards for my research, none means as much to me as the Eddy Award. This Award recognizes what I have spent most of my career doing and comes from the people who know me best. I have sat in CPDD meeting audiences for many years, watching others receive the Award, and have wondered how they felt. I can now tell you it is an unbelievable high. My brain dopamine level must be very high at this moment. I want to thank the College on Problems of Drug Dependence, the Awards Committee, and Mike Kuhar for making the effort to nominate me for this Award and for such a glowing introduction.

One benefit of the Award is that I now have the opportunity to tell you about some of the research I have done the last few years. As the title indicates, I am going to present results of our efforts to design and develop pharmacotherapies for substance abuse. There are a number of targets one could choose to use for developing pharmacotherapies for substance abuse. For my studies I chose the most obvious targets of monoamine transporters, opioid receptors, and nicotinic receptors. Since I could not present all we have done in the time allotted, I chose to mainly present studies we have done in the last few years. Mike covered some of the earlier work in his introduction. I will provide a little more detail of how each target was studied.

Monoamine Transporters

My research with monoamine transporters started with a telephone call from Mike Kuhar asking if I could synthesize a radiolabeled compound for him. During this discussion, he informed me about his hypothesis that the dopamine transporter (DAT) was the cocaine-binding site (receptor) responsible for its reinforcing properties. I found this very interesting and suggested that we might be able to help him gain additional evidence for his hypothesis, which led to a collaboration with Mike that is still on-going 18 years later. Since a true receptor should be stereoselective, the first thing we did was synthesize and test all eight possible cocaine isomers. We found that only natural cocaine had appreciable affinity for the DAT; the other seven isomers were 60–600 times weaker.[1] These studies, along with other in vitro and behavioral pharmacology studies from our laboratories as well as those from other laboratories, established that the cocaine-binding site on the DAT was important to cocaine's reinforcing properties. With this established, we proceeded to characterize the binding site through a structure activity relationship (SAR) study with the long-range goal of developing pharmacotherapies to treat cocaine abuse. One of the most important findings from our early SAR studies on cocaine analogues was that the isopropyl and phenyl esters, RTI-14 and RTI-15, respectively, while similar to cocaine in their affinity for the DAT, showed much lower affinity at the serotonin and norepinephrine transporters (SERT and NET, respectively).[2,3] This information was used to design and prepare DAT-selective analogues in the cocaine series as well as the 3-phenyltropane series, which follows. Another important finding from the cocaine SAR study was that cocaine analogues with very large 2β-ester groups, such as the *p*-aminophenylethyl ester group in RTI-65, retained affinity for the DAT similar to that of cocaine. This SAR information led to the design, synthesis, and evaluation of a number of cocaine and 3-phenyltropane analogues with diverse groups in the 2-position of the tropane ring.[4]

In very early studies, Clarke and co-workers reported that the monoamine uptake inhibitor 3-phenyltropane analogues, WIN 35,065-2 and WIN 35,428, were five- to six-fold more potent than cocaine in behavioral studies.[5,6] Subsequent studies, including our own, made similar observations with other drug-induced behaviors. We synthesized [^{3}H]WIN 35,065-2 and showed that it had a better specific-to-non-specific binding ratio than cocaine.[7,8] Importantly, in vivo binding studies showed that [^{3}H]WIN 35,065-2 had a much slower onset and longer duration than [^{3}H]cocaine. These advances prompted us to conduct a SAR study on the 3-phenyltropane class of dopamine (DA) uptake inhibitors.

As we began collecting DAT binding and behavioral pharmacology data, our attention turned to the development of 3-phenyltropane analogues as indirect dopamine agonists for pharmacotherapies for cocaine addiction. In general, the 3-phenyltropanes showed high affinity for the DAT, entered the CNS slower, and possessed a longer duration of CNS activity than cocaine. It was thought these properties were needed for a suitable indirect dopamine agonist pharmacotherapy. In later studies other investigators suggested that low locomotor sensitization would also be a desirable property. The following provides a brief review of the research that led to the selection of a clinical candidate and then a little more detail about the properties of the selected 3-phenyltropane analogue.

Early in our studies we reported that the 4'-chloro-, 4'-bromo-, 4'-iodo-, and 4'-methylphenyl and 3'-methyl-4'-chlorophenyl analogues, RTI-31, RTI-51, RTI-55, RTI-32, and RTI-112, respectively, showed high affinity for the DAT as well as the SERT and NET and were significantly more potent than cocaine in locomotor activity.[9,10] In vivo binding studies revealed that the dose that produced the EC_{50} value of behavioral effects produced near maximal occupancy (>50%) of the DAT.[10] RTI-55, RTI-31, RTI-32, and RTI-112 were shown to substitute for cocaine in rats trained to discriminate cocaine from saline.[10,11] Pretreatment of rats, squirrel monkeys, and rhesus monkeys trained to self-administer cocaine with RTI-112 resulted in a reduced intake of cocaine.[12,13] Combining the results with previous studies on RTI-112 showed that 3-phenyltropane analogues that possessed high affinity for all three monoamine transporters possessed pharmacological properties needed for an indirect dopamine receptor agonist pharmacotherapy.

At the same time, we were studying RTI-112, we were also investigating the possibility that a DAT-selective 3-phenyltropane analogue might also possess pharmacological properties needed for an indirect dopamine receptor agonist pharmacotherapy. 3β-4-Chlorophenyltropane-2β-carboxylic acid phenyl ester (RTI-113), which was highly selective for the DAT,[3] produced potent and long-lasting locomotor activity in mice and cocaine-like discriminative effects in rats.[14,15] Pretreatment with RTI-113 produced reduction of cocaine self-administration in rats, squirrel monkeys, and rhesus monkeys.[16-18] These studies supported the hypothesis that a 3-phenyltropane analogue that targeted only the DAT could serve as an indirect dopamine agonist pharmacotherapy to treat cocaine abuse and dependence.

Since a 3-phenyltropane analogue that possessed high-affinity for the DAT with weak affinity for the SERT and NET would have high potential as a useful pharmacotherapy for treating cocaine addicts without deleterious side effects, we devoted a large part of our effort to developing DAT-selective 3-phenyltropane analogues. Over the last several years, we synthesized and evaluated over 800 3-phenyltropane analogues for binding at the DAT, SERT, and NET.[19-21] Forty-seven (47) compounds showed selectivity for the DAT relative to the SERT and NET. As stated earlier, the ideal pharmacotherapy should differ from cocaine in several keys ways: first, it should have a slower onset of action; second, it should have a longer duration of action; third, a clinical candidate should show low sensitization; and fourth, it should be less stimulatory than cocaine at peak doses. In addition, a clinical candidate should be orally active. As a direct test for potential efficacy in humans, the compound should substitute for cocaine in animal models and should block cocaine self-administration in both rats and rhesus monkeys. In order to identify 3-phenyltropane analogues that possessed pharmacological properties suitable for further consideration, the 47 compounds were first evaluated for locomotor activity in mice and cocaine discrimination in rats, followed by studies of the five best compounds on the effects of self-administration of cocaine in a rat and rhesus monkey model. The studies revealed that 3β-(4-chlorophenyl)-2β-[3-(4'-methylphenyl)isoxazol-5-yl]tropane (RTI-336) possessed the best overall balance of pharmacological properties.

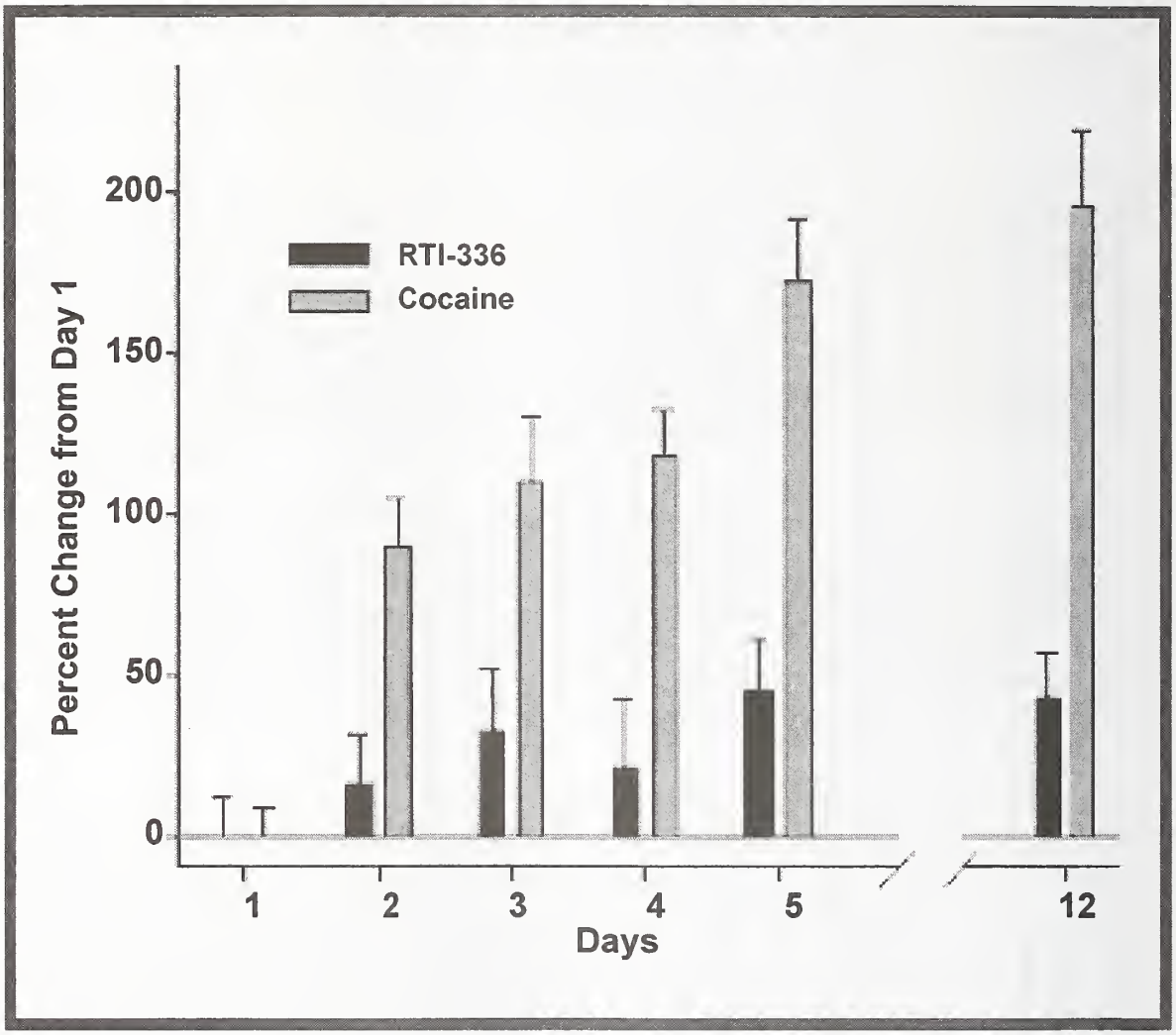
RTI-336's locomotor activity efficacy in mice was less than that of cocaine (Table 1), and RTI-336 did not show sensitization (Figure 1). Locomotor studies in mice, time-course stimulant

Table 1. Comparison of locomotor activity of RTI-336 to that of cocaine in mice

Compd RTI No.	Locomotor Activity (i.p.)				Locomotor Activity (p.o.)			
	Peak Time[a] (min)	ED_{50}[b] mg/kg	Percent Cocaine[c]	Duration[d] (h)	Peak Time[a] (min)	ED_{50}[b] mg/kg	Percent Cocaine[c]	Duration[d] (h)
Cocaine	0–30	21	100	<2				
RTI-336	70–100	4.8	71	>4	60–90	10	77	>4

[a] 30-min period during which the compound produced its maximal effect. [b] Dose to produce 50% of the compound's maximal effect. [c] Compound's maximal effect as a percent of cocaine's maximal effect. [d] Time during which activity returned to baseline level.

Figure 1. Comparison of cocaine sensitization to that of RTI-336 in mice



effects, microdialysis in squirrel monkeys, and PET imaging studies in rhesus monkeys all showed that RTI-336 had a much slower entry into the brain and pharmacological onset of action than cocaine and also had a longer presence in the brain and duration of action relative to cocaine.

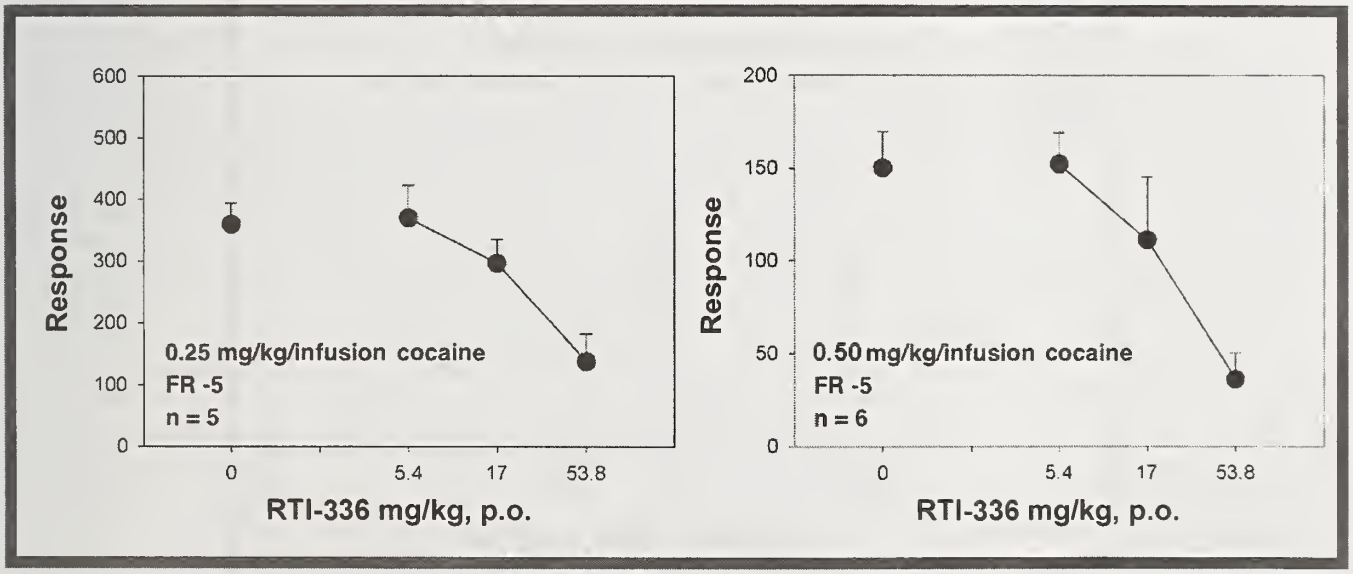
As expected for an indirect dopamine agonist, RTI-336 was able to replace cocaine in a drug discrimination test in rats using either i.p. or p.o. administration (Table 2). In addition, pretreatment (p.o.) with RTI-336 reduced cocaine self-administration in rats (Figure 2). Pretreatment with RTI-336 also produced dose-dependent reduction in cocaine and food maintained responding in rhesus monkeys (Figure 3). ED_{50} doses of RTI-336 resulted in 90% DAT occupancy. No adverse behavioral effects were observed at any pretreatment dose of RTI-336. RTI-336 maintained drug self-administration in monkeys trained to self-administer cocaine but was not as effective as cocaine in maintaining high rates of responding across a range of doses. No adverse behavioral effects were observed at any substitution dose of RTI-336. Doses of RTI-336 that maintained peak rates of responding resulted in 62% DAT occupancy.

Table 2. Drug discrimination effects of RTI-335 in rats[a]

	Drug Discrimination	
Compd	ED_{50}, i.p. mg/kg	ED_{50}, p.o.[b] mg/kg
RTI-336	5.6	5.8

[a] DATA from NIDA CTDP. [b] Full generalization lasts up to 180 min and partial generalization at 360 min.

Figure 2. Effect of RTI-336 on cocaine self-administration in rats



These studies, combined with a highly favorable in vitro and in vivo toxicity profile, led to RTI-336's selection as a clinical candidate. Table 3 summarizes the overall profile for RTI-336. The IND is being prepared; if approved by FDA, Phase I studies could begin early in 2007.

As Mike indicated in his introduction, our research provided several new radioligands for studying the DAT.[8,22-27] [^{125}I]RTI-121 and [^{125}I]RTI-229 were developed as potent and selective radioligands for the DAT[24,28,29] and [^{125}I]RTI-55 as a useful radioligand for biochemical studies of both the DAT and SERT.[23,30-36] [^{125}I]RTI-55 and [^{125}I]RTI-121 are both marketed by Perkin Elmer and are used by many scientists in their own research. Both RTI-55 and RTI-121 have been labeled with iodine-123 and carbon-11 and have been used in Single Photon Emission

Figure 3. Effects of RTI-336 on cocaine- and food-maintained behavior in rhesus monkey

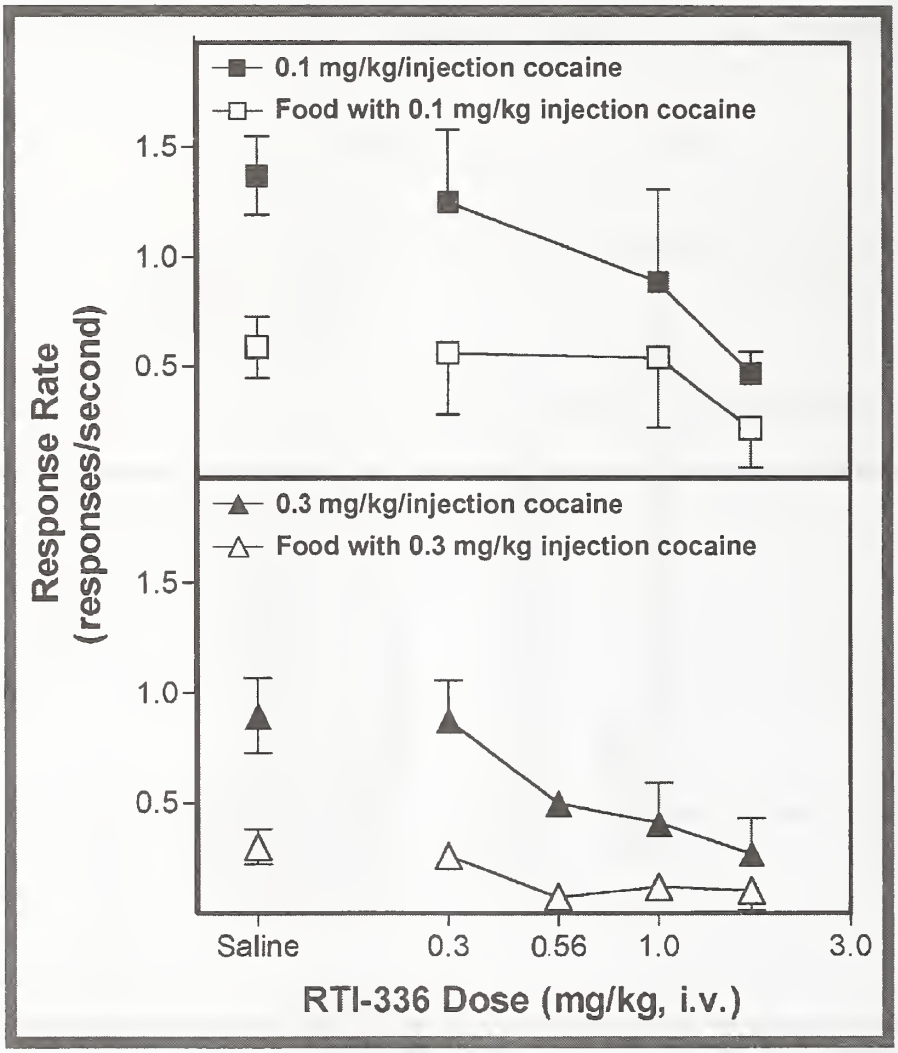


Table 3. Summary of RTI-336 profile

- Selective for DAT relative to SERT and NET.
- Locomotor activity less than that of cocaine with low sensitization.
- Orally active in locomotor, drug discrimination, and self-administration assays.
- Reduced cocaine self-administration in rat and monkey.
- High DAT occupancy required for therapeutic effectiveness.
- Shows slow onset and long duration of action in rodent and monkey.
- Abuse potential may be less than cocaine.
- Little interaction with other receptor systems and cytochrome P450 enzymes.
- Excellent therapeutic ratio.

Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging studies in rats, baboons, and humans. These studies led to the development of [^{123}I]RTI-55 (Dopascan) as a diagnostic agent for Parkinson's Disease.[30,37-41] Thousands of patients have been diagnosed. Several other investigators have used [^{123}I]RTI-55 for neuroimaging studies related to cocaine abuse.

I also developed several 3-phenyltropane analogues that bind irreversibly to the cocaine binding site on the dopamine transporter; these proved highly useful in biochemical studies. RTI-82, a photoaffinity ligand, and RTI-76, an irreversible ligand, have been used to more fully characterize the in vitro and in vivo pharmacology of the dopamine transporter.[42-50]

3-Phenyltropane analogues were developed that have greater potency and selectivity for the SERT than Prozac and paroxetine and, thus, have potential use as antidepressants.[21,51-53] One of the high affinity-selective analogues is 3β-(4-ethyl-3-iodophenyl)nortropane-2β-carboxylic acid methyl ester (EINT). [^{125}I]EINT is a useful radioligand for the characterization of SERT.[54,55] The irreversible ligand RTI-76 has been used to further characterize the in vivo pharmacology of the serotonin transporter.[56] A 3-phenyltropane fluorescent ligand RTI-233 was designed, synthesized, and used to conduct biophysical characterization of the cocaine binding site on the serotonin transporter.[57,58]

Other studies showed that 3α-(3'-fluoro-4'-methylphenyl)nortropane-2β-carboxylic acid methyl ester (RTI-539) was a 3-phenyltropane analogue selective for the norepinephrine transporter.[59,60]

Opioid Receptors

My opioid receptor research program resulted from a number of discussions with Denny Zimmerman from Eli Lilly and Company. Denny and I were members of a NIDA review committee, which gave us a chance to discuss our respective research interests at the three committee meetings each year. I learned enough from these discussions to submit a grant application to NIH entitled "Selective Opioid Antagonist as Medications for Drug Abuse." The grant was funded, allowing me to broaden my research efforts to include studies of opioid receptors. A major goal of our proposal was to develop potent and selective κ opioid receptor antagonists that possessed better in vivo pharmacological properties than those that were then available. The reason for my interest in κ opioid receptor antagonists was that a number of reports suggested that they would be useful in treating stress and depression and, thus, would be useful for treating stress-induced relapse to taking cocaine, methamphetamine, opiate, and other substances of abuse. Applying new technologies to the *N*-substituted *trans*-3,4-dimethyl-(3'-hydroxyphenyl)piperidine class of opioid antagonist led to a κ opioid receptor antagonist, which we named JDTic. It is an extremely potent and selective antagonist of the opioid kappa receptor with a K_e = 0.01 nM in the [^{35}S]GTPγS in vitro functional assay with selectivities of 341- and 7930-fold relative to the μ and δ opioid receptors.[61] JDTic antagonized κ agonist U50,488H-induced polyuria in rats using subcutaneous and oral administration and antagonized κ agonist enadoline-induced antinociception in mice using subcutaneous or oral administration but had no effect on μ agonist sufentanil-induced antinociception and antagonized U50,488H-induced analgesia in squirrel monkeys using intramuscular administration.[62,63] These studies showed that JDTic was a potent and κ selective opioid receptor antagonist in mice, rats, and monkeys and was the first orally active κ antagonist.[62,63]

Due to the potential of the κ antagonist to attenuate the effects of stress and that a stressor could precipitate relapse in cocaine use, JDTic was evaluated in a rat stress (foot shock)-induced relapse model and the forced swim test (FST). After oral administration, JDTic blocked stress-induced reinstatement of cocaine-seeking behavior but did not affect cue or cocaine-induced reinstatement in the relapse model, and decreased immobility time, and increased swimming time in the FST at doses as low as 0.3 mg/kg (s.c.).

JDTic was evaluated for its prophylactic effects on the development/expression of ethanol seeking and relapse consumption of ethanol in ethanol-preferring rats. JDTic dose-dependently prevented expression of ethanol Pavlovian Spontaneous Recovery (an animal model of alcohol seeking), reduced expression of an Alcohol Deprivation Effect (an animal model of relapse) but had no effect on ethanol-maintenance responding.

JDTic was not mitogenic, showed very low hERG activity, low potency for inhibiting cytochrome P-450 enzymes, and was very clean in NovaScreen profiling. No deaths were observed when a 1000 mg/kg of JDTic was administered by oral gavage to rats and squirrel monkeys. Combining these results with its activity in the rat cocaine relapse model and FST led to the selection of JDTic as a clinical candidate as a potential pharmacotherapy to prevent relapse to cocaine use. Table 4 summarizes the overall profile for JDTic. JDTic is being developed for Phase I clinical studies under a NIDA SPIRDAP grant.

Table 4. Summary of overall profile for JDTic

- JDTic selectively reverses the effects of kappa agonists in three different animal models.
- JDTic prevented resumption of cocaine-seeking precipitated by a stressor.
- JDTic is the first orally active kappa antagonist.
- JDTic decreased immobility and increased swimming consistent with an antidepressant-like effect in the rat FST.
- JDTic blocked the expression of ethanol PSR and inhibited the expression of ADE.
- JDTic has a favorable in vitro and in vivo toxicity profile.
- JDTic may have potential use in preventing cocaine or ethanol relapse and treating depression.

The success with JDTic prompted us to look for other chemotypes that might show potent and selective κ opioid receptor antagonist activity. Taking advantage of the information we gained from the development of JDTic from the trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class, we developed *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)-7α-3-(piperidinopropanamido)morphan [(-)-KAA1] as the first potent and selective κ opioid receptor antagonist from the 5-arylmorphan class of opioids (Table 5).[64] (-)-KAA1 had a K_e = 0.24 nM in the [^{35}S]GTPγS assay and was 175- and 138-fold selective for κ receptor relative to the μ and δ opioid receptors. The 4β-methyl group provided the opioid receptor antagonist activity, the 7α-[3-(1-piperidinopropanamido], the κ selectivity, and the *N*-phenylpropyl, the increased potency. This discovery was followed by the design, synthesis, and development of several other more potent and selective analogues from this chemotype. The most potent and selective κ opioid receptor antagonist was *N*-(2-methylphenylethyl)-4β-methyl-5-(3-hydroxyphenyl)-7α-[3-(1-tetrahydroisoquinoline propanamido]morphan (MTHQ).[64] This analogue had a K_e = 0.04 nM and was 700- and 625-fold selective for the κ opioid receptor relative to the μ and δ opioid receptors (Table 5).

Table 5. Kappa opioid receptor selective 5-phenylmorphan antagonists

	K_e, [^{35}S]GTPγS (nM)				
Compd	μ	δ	κ	μ/κ	δ/κ
(-)-KAA1	42	33	0.24	175	138
MTHQ	28	25	0.04	700	625

In preliminary studies to develop other additional chemotypes of selective κ opioid receptor antagonist, we investigated *N*-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinalines.[65] The most potent and selective compound thus far developed was racemic *N*-[4a-(3-hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinoline-6-yl]-3-(piperidin-1-yl)propionamide, which had a K_e of 0.27 nM at the κ opioid receptor with 154- and 46-fold selectively relative to the μ and δ receptors, respectively. In this case, the κ opioid receptor antagonist activity resulted from the presence of 8a-methyl group.

Since δ opioid receptor antagonists were known to antagonize the side effects of μ opioid agonist such as morphine, we were interested in developing new chemotype potent and selective δ opioid receptor antagonist. By starting with the enantiomeric 5-phenylmorphan isomer used to develop (-)-KAA1 and MTHQ, we developed (+)-*N*-phenylpropyl-5-(3-hydroxyphenyl)-7α-(2-phenyl-2-cyclopentanecarboxamide)morphan [(+)-KF4], which had a K_e = 0.15 nM for the δ receptor and 58- and 119-fold selective for the δ receptor relative to the μ and κ opioid receptors (Table 6).[66] Replacement of the spiropentyl group in (+)-KF4 with two methyl groups gave Delmorphan-A, which had a K_e = 0.1 nM and was now 103- and 132-fold selective for the δ opioid receptor relative to the μ and κ opioid receptors. Both (+)-KF4 and Delmorphan-A were inverse agonists at the δ opioid receptor with IC_{50}s of 1.8 and 0.4

nM, respectively (Table 7). Since NTI is a neutral δ antagonist, (+)-KFA4 and Delmorphan-A provide a new type of δ opioid receptor antagonist for study.

Table 6. Delta opioid receptor selective 5-phenylmorphan antagonists

	K_e, [^{35}S]GTPγS (nM)				
Compd	μ	δ	κ	μ/κ	δ/κ
NTI	33	0.21	16	157	77
(+)-KFA4	8.7	0.15	18	58	119
Delmorphan-A	10.3	0.1	13.2	103	132

Table 7. Delta opioid receptor inverse agonist

Compd	IC_{50} (nM)	% of basal binding
PTX		61
ICI 174,864	83	75
(+)-KFA4	1.8	70
Delmorphan-A	0.4	64

Nicotinic Receptors

John Daly and NIH colleagues reported the isolation, structural characterization, and potent analgesic activity of 2-exo-2-(2'-chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (epibatidine). Subsequent studies showed that the analgesic activity resulted from interaction with nicotinic acetylcholine receptors (nAChRs). The unique structure and biological activity of epibatidine generated considerable interest in the compound and precipitated the development of numerous routes for its syntheses, including one from our laboratory. Our synthesis proceeded through a versatile intermediate allowing us to make a diverse set of epibatidine analogues. At about this time, NIDA became interested in the nAChR and the development of medications to treat smokers. In response to this interest, Billy Martin and I put together an NIDA collaborative grant application entitled "Development of Ligands for Nicotinic Receptors," which combined his in vivo testing capabilities with my synthetic abilities. The grant was funded, and over the last few years our efforts provided some highly interesting results. We first studied the effect of replacing the 2'-chloro group in epibatidine and found that the 2'-hydrogen and 2'-fluoro-, 2'-bromo-, and 2'-iododeschloroepibatidine all possessed essentially identical nAChR K_is in a binding assay and were potent nAChR agonist in the mouse tail-flick test. The ^{18}F-labeled derivative [^{18}F]NFEP of 2'-fluorodeschloroepibatidine was shown to bind with high specificity and affinity to nAChR and to provide exquisite images of the thalamic nAChR in the baboon using positron emission tomography (PET). However, due to its potent nAChR agonist activity, it was not advanced to human PET studies.[67]

The above studies were followed by the synthesis and biological evaluation of 3'-substituted deschloroepibatidine analogues. The 3'-fluoro-, 3'-chloro-, 3'-bromo-, 3'-iodo-, 3'-amino-, 3'-vinyl-, and 3'-ethynyldeschloroepibatidine analogues had K_is = 0.02 to 0.26 nM at α4β2 nAChR.[68] Even though some of these compounds possessed α4β2 nAChR binding affinity equal to that of epibatidine, all the compounds were weak agonists in tail flick and hot plate tests in mice. In contrast, they were functional antagonists in nicotine-induced antinociception. For example, 3'-iododeschloroepibatidine had a K_i = 0.059 nM at α4β2 nAChR and an agonist ED_{50} and an antagonist AD_{50} of 0.8 and 0.0001 mg/kg in the tail flick test, respectively. Adding an *N*-methyl group to give *N*-methyl-3'-iodo-

deschloroepibatidine (NMI-EPB) increased binding affinity (K_i = 0.029 nM) and gave a 2.5-fold increased potency in antagonist activity.

PET studies in baboon using [^{11}C]NMI-EPB revealed that it penetrated the blood brain barrier, achieved equilibrium fast, and localized selectivity in brain regions consistent with nAChRs and fast kinetics.[69] Thus, [^{11}C]NMI-EPB may have potential for use in imaging studies in humans. The presence of an iodine atom in NMI-EPB will also allow labeling with iodine-123 for SPECT studies.

The 2',3'-disubstituted epibatidine analogues possessing 3'-fluoro, 3'-chloro, 3'-bromo, 3'-iodo, and 3'-amino substituents had K_is of 0.008 to 0.027 nM compared to 0.026 for epibatidine at the α4β2 nAChR.[70] However, the analogues with 3'-fluoro, 3'-chloro, and 3'-amino possessed significantly higher affinity (K_i = 1.1 to 13.9 nM) for the α7 nAChR relative to epibatidine (K_i = 198 nM). Analogues that possessed electron-withdrawing groups in both the 2'- and the 3'-position showed high affinity for the αβ nAChR receptor in vitro and showed agonist activity in vivo. However, the agonist activity did not correlate well with their binding affinities. The most interesting compound studied was the 2'-chloro-3'-amino analogue, which had both antagonist and agonist properties.

Using the same intermediate we used to prepare epibatidine and all the above analogues, we synthesized several 2'-fluoro-3'-(substituted phenyl)deschloroepibatidine analogues.[71] All of the compounds possessed high affinity for the α4β2 nAChR. Surprisingly, only one of the compounds showed agonist effects in a pain test in mice even when tested at 10–15 mg/kg. In contrast, all of the compounds were potent functional antagonist of nicotine-induced antinociception. One of the more interesting analogues was 2'-fluoro-3-(4-nitrophenyl)deschloroepibatidine (4-nitro-PFEB), which possessed a K_i = 0.009 nM at α4β2 nAChR, and, thus, has more than 4000 times higher affinity than the standard competitive antagonist dihydro-β-erythroidine. 4-Nitro-PFEB inhibited acetylcholine-induced currents at human α4β2 nAChR with an IC_{50} = 0.1 nM, which was 17 times more potent than β-dihydroethroidine.[72] Its IC_{50} at α4β2 nAChR was 64 μM compared to an IC_{50} = 22 nM for β-dihydroethroidine. Thus, 4-nitro-PFEB was a highly potent and selective α4β2 nAChR antagonist. It was also a potent antagonist of nicotine-induced antinociception in the mouse tail-flick test (AD_{50} = 0.003 mg/kg).

When we started our nAChR program, the protein [^{125}I]α-bungarotoxin was the standard for studying the α7 nAChR in vitro. Unfortunately, it was difficult to use and was not suitable for in vivo studies. We developed [^{125}I]iodomethyllycaconitine ([^{125}I]iodoMLA) as a more potent and selective α7 nAChR radioligand.[73]

In today's presentation, I have largely presented studies that have been conducted with some of our more interesting compounds. I want to thank a highly talented group of past and present postdoctoral fellows (some of whom have taken positions at RTI), who were responsible for the synthesis of the compounds. I want to thank many collaborators both at RTI and at other institutions for their numerous contributions. Even though she is not here to see the result of her efforts, I want to thank my wife Sara for her total support. I have spent my whole professional career at RTI and am most appreciative of the facilities and environment provided for my research. All the research described in this presentation was supported by the National Institute on Drug Abuse (NIDA), and I thank them for their support. Lastly, I want to express again how honored I am to receive the 2006 CPDD Nathan B. Eddy Memorial Award.

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MARIAN W. FISCHMAN LECTURESHIP RECIPIENTS

2006	**Lynda Dykstra**
2005	**Mary Jeanne Kreek**
2004	**Nancy K. Mello**
2003	**Maxine L. Stitzer**
2002	**Chris-Ellyn Johanson**

Introduction of Linda A. Dykstra for the 2006 Marian W. Fischman Lectureship Award

Stephen G. Holtzman

Department of Pharmacology, Emory University School of Medicine, Atlanta, GA

It is with great pleasure that I introduce this year's recipient of the Marian W. Fischman Lectureship Award Linda A. Dykstra.

Linda has made significant and continuous contributions in the areas of research, service, and training in the field of drug abuse. As anyone who has been on this planet for more than a few days know, Linda has been a major contributor to the behavioral pharmacology literature, especially that relating to opioid drugs. She, together with Dr. Don McMillan and other assorted henchmen and a series of trainees, developed a shock-titration procedure for studying the behavioral and antinociceptive effects of opioids in squirrel monkeys (1-4). This procedure led to important characterizations of the effects of *mu*- and *kappa*-opioid agonists in a non-human primate, and provided important new insights into the efficacy of partial agonists and mixed agonist-antagonists.

Other areas of opioid behavioral pharmacology that Linda has contributed to include the discriminative stimulus effects of *mu*- and *kappa*-opioids (5-8) and tolerance and cross-tolerance to *mu*-opioid agonists (9-11) in several animal species. And some of those studies represent virtually the only work of its type performed on non-human primates.

Linda's broad range of research interests and expertise extends to the immunopharmacology of opioid drugs, where, in collaboration with Dr. Donald Lysle, she has been making novel and important contributions to that literature for more than a decade (12-14). A few years ago she spent time as a visiting professor in the laboratory of Marc Caron at Duke University. That stint resulted in an ongoing collaboration in which Linda contributed fundamental behavioral pharmacological approaches for studying genetically-modified mice lacking cellular components essential to the actions of morphine or cocaine (15, 16). As a consequence, the research project has been elevated from strictly molecular biological observations to an integrated, and in my opinion, a more productive approach to the whole riddle of the cellular substrates mediating drug effects relevant to abuse potential. Linda's prodigious research activities have resulted in 150 or so peer-reviewed journal articles.

Linda's exemplary service activities span the spectrum from the institutional to the national level, and provide further evidence of her stature and reputation. At the institutional level Linda serves as Dean of the Graduate School, a position she has held for 10 years. At the state level she serves on the Executive Board of the North Carolina Association for Biomedical Research. And at the national level she chaired the Division for Neuropharmacology of the American Society for Pharmacology and Experimental Therapeutics (ASPET), among many other positions. Past service includes terms on NIH study sections and NIDA's National Advisory Council and membership on editorial boards, not to mention a leadership role in CPDD. Linda served as a member of the Board of Directors, as well as a member of the Executive Committee during her 3-year sequence as president-elect, president, and past president.

Last but not least, Linda has been a supportive mentor for pre- and postdoctoral trainees in the behavioral pharmacology of abused drugs, for which she was recognized by CPDD with the 2005 Mentorship Award She currently directs a NIDA-sponsored Institutional Predoctoral Training Program, and has helped launch many familiar names into notable careers in drug abuse research.

For these reasons and many more Linda is uniquely qualified to receive the Marian W. Fischman Lectureship Award. And how fitting the honor in view of the fact that Linda was a contemporary of Marian while they were graduate students at the University of Chicago. She is, in all respects, the "outstanding woman scientist in drug abuse research" that the award was intended to honor. I now present to you my colleague and long-time friend Linda Dykstra, who will give the 2006 Marian W. Fischman Lectureship Award lecture.

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OPIOID ANALGESICS: MENTORS, MONKEYS and MICE
2006 Marian Fischman Lecture
College on Problems of Drug Dependence
June 19, 2006
Linda Dykstra
University of North Carolina at Chapel Hill

Let me begin my thanking President Kathy Cunningham, long-time colleague Steve Holtzman and the members of the CPDD Awards Committee for this great privilege. I couldn't be more pleased than to speak in honor of the grace, the joy and the commitment that Marian Fischman brought, not only to our own friendship, but also to the greater tradition of collegiality that we all cherish.

By way of providing some history, I should tell you that Marian and I were not colleagues in the traditional way. We never conducted an experiment together, and our names don't appear together on any publications. I don't recall ever reviewing any of Marian's many, beautifully-conducted experiments or commenting on her grant proposals, and it is likely that Marian did not review any of my own research contributions. Marian's most notable research was conducted in human subjects with emphasis on cocaine; my own research employed animal models and focused on the opioids. Nevertheless, Marian and I were colleagues, in that gratifying way in which many of us here today are colleagues.

My friendship with Marian began in graduate school at the University of Chicago where we were both students in the Psychology Department. Although we were trained in different laboratories, we took many of the same courses and benefited from the same mentors. After graduate school, our professional and personal contacts continued, as together with another colleague and friend, Chris-Ellyn Johanson, we often "hung out together" at professional meetings such as those of the Committee on Problems of Drug Dependence, the Behavioral Pharmacology Society, the Association of Pharmacology and Experimental Therapeutics and the American College of Neuropsychopharmacology. Throughout it all, I admired Marian always for her great style, her commitment to family and her ground-breaking research.

As the years go by, and CPDD continues to host the Marian W. Fischman Lectureship Award, it will be less likely that the recipient of the award will have enjoyed a personal association with Marian and benefited directly from her generous spirit. Yet it is certain that the recipient, whoever they might be, will have benefited from multiple mentoring relationships, both top/down as in mentor to student, as well as student to student; colleague to colleague. Therefore, I believe the most enduring aspect of this award goes beyond our collective memories of Marian's contributions, for it provides recognition of what it means to benefit from, and to be a colleague.

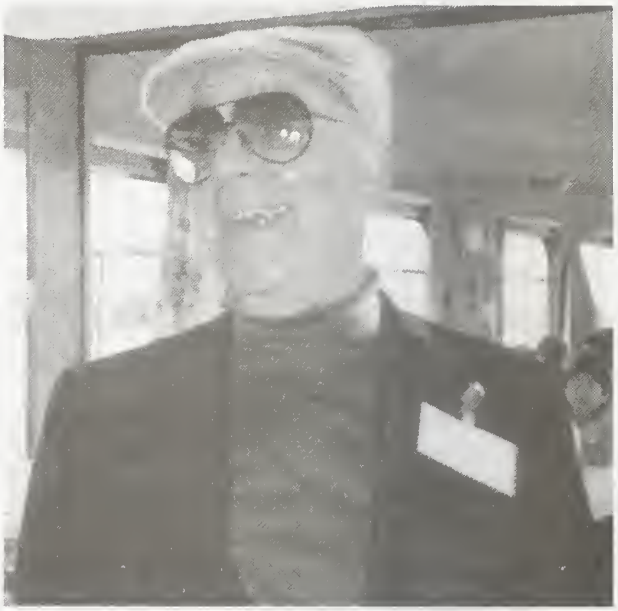
Let me begin by attempting to blend some scientific findings from my own academic journey with a few recollections of the collegial relationships that I encountered along the way, particularly those that provided the foundation for the research program that has occupied me and a large number of students within my laboratory over the last 30+ years. Given time constraints and in due respect to the broad expertise of CPDD members, I've elected to tell this story by focusing on one area of interest in our laboratory, namely, the behavioral pharmacology of opioid analgesics. In doing so, I will try to follow what one might call a top/down progression, starting with some background drawn from almost three decades of research in monkeys, to our more current attempts to design meaningful investigations in genetically-altered mice.

Chicago Years: LSD and Signal Detection Analysis

My training in behavioral pharmacology began when I was a graduate student at the University of Chicago in the late 1960s where I was part of a remarkable group of scientists who were my first mentors and colleagues. Among them were fellow graduate students, Marian Fischman, Chris Johanson and Klaus Miczek, and postdoctoral fellow Bob Balster. Our mentors included some very well know scientists, Bob Schuster, Jim Appel and Lew Seiden, all shown in Fig. 1

FIGURE 1: CHICAGO COLLEAGUES

Linda Dykstra, Marian Fischman and Chris Johanson



Jim Appel

Bob Balster, Jim Woods, Klaus Miczek, and Bob Schuster

Lew Seiden

I actually went to the University of Chicago as a Ford Foundation Fellow, to obtain a masters degree in English Literature, and I tell you that so you know that one can never know the course of one's career path. Plans often change along the way and thanks to the notable flexibility of the University of Chicago, I was allowed to move from English Literature, to Psychology and ultimately to a research rotation in Jim Appel's laboratory, within the Department of Psychiatry.

In Jim Appel's laboratory, I benefited from his interest in LSD (lysergic acid diethylamide), one of the newest drugs on the experimental scene at that time. My dissertation examined the effects of LSD on auditory and visual perception in rats, pigeons and a few squirrel monkeys, using what was a novel approach at that time, namely Signal Detection Analysis. We were drawn to this approach since it provided a way to measure both an organism's sensitivity (i.e., ability to detect) a stimulus apart from factors that might influence an organism's bias to respond in one way or another. Given ongoing interest in LSD-induced perceptual alterations, it seemed possible that Signal Detection Analysis might provide a way to understand the nature of those alterations (Dykstra and Appel, 1974).

Given this focus on LSD, I really didn't pay much attention to the opioids at that time. Nevertheless, our laboratory was located in an old 3-story walkup building, directly above one of the very first methadone maintenance clinics in the country, then directed by Bob Schuster. Perhaps that experience was responsible for my subsequent interest in opioids. Whatever it was, my Chicago experience certainly provided an inspiring beginning.

Enter the Opioids

Those early experiences, coupled with my interest in drug-induced alterations in perceptual behavior prepared me to take particular advantage of yet another set of colleagues, when I moved to the University of North Carolina as a postdoctoral fellow. There I worked closely with, my postdoctoral advisor, Don McMillan, as well as a close postdoctoral colleague, David Leander. Again, I benefited from another committed group of mentors, including some of CPDD's best known scientists, Lou Harris, Bill Dewey and Billy Martin, shown here in two rare photo opportunities.

FIGURE 2 NORTH CAROLINA COLELAGUES

Don McMillan, Billy Martin, Bill Dewey and Lou Harris

Dave Leander

One can't remain a postdoctoral fellow forever, and in my case, this period was cut very short by good fortune, namely the opportunity to become part of the Psychology faculty at UNC/Chapel Hill. It was in this context that I coupled my graduate school investigations of drug-induced alterations in sensation and perception with what I learned about opioid analgesics from my colleagues in the UNC Pharmacology Department. Encouraged by my Carolina colleagues, I joined the quest for a "better analgesic"—a drug with pain relieving properties, as good as those of morphine, but less likely to produce tolerance, dependence and respiratory depression. In this search, drugs of diverse chemical structure were being synthesized and a number had promise, including drugs with mixed agonist/antagonist profiles as well as others with selective activity at different opioid receptor types.

Psychology and a New Emphasis on Behavior

Within my own laboratory, now situated across campus from my colleagues in Pharmacology, we approached these questions, not as chemists, designing new drugs, but rather as behavioral pharmacologists, interested in interactions between the behavioral and the pharmacological effects of drugs. As a result, we placed heavy emphasis on developing and perfecting behavioral procedures that provided clear, consistent data. This emphasis on developing precise behavioral procedures harkens back to the intellectual tradition that I shared with Marian Fischman at Chicago. Thanks to the influence of individuals such as Bob Schuster, Lew Seiden and Jim Appel, we quickly came to appreciate the power of combining precise behavioral measures with careful pharmacology, as described in one of the very first textbooks in this area, Seiden and Dykstra, Psychopharmacology: A Biochemical and Behavioral Approach (1977).

In this context, one of those procedures was the primate titration procedure. Inspired by the early work of Victor Laties and Bernie Weiss, our laboratory set out to develop a primate model of analgesia, ideally a procedure that would allow us to separate drug-induced alterations in pain perception from other effects, not necessarily related to pain perception. This question was clearly driven by my earlier research regarding LSD-induced alterations in perceptual processes.

Though we no longer employ the monkey titration in our laboratory today, it was certainly central to our early research and proved to be particularly amenable to pharmacological questions. What is important to note is that, unlike many rodent procedures that require a less integrated, reflexive response, in the titration procedure the monkey controls, rather than responds to, the nociceptive stimulus.

Briefly, the procedure we used involved delivering low, but gradually increasing levels of shock to the monkey's tail in incremental steps and allowing the monkey to control the stimulus intensity by responding on a lever. In short, the monkey "titrated the intensity", presumably maintaining the stimulus at a comfortable level, only allowing it to increase when a drug, such as morphine, had altered the nociceptive properties of the stimulus. As I have emphasized on numerous occasions, because I believe it is so important, the procedure met all the requirements of the Society for the Study of Pain in Animals. The intensity was no higher than it needed to be to obtain reliable data. There were safe guards in place to terminate the stimulus, if necessary, and the experimenter had experienced the stimulus. The strength of this procedure rested on the fact that the level at which monkeys maintained the stimulus (median shock level, MSL) could be measured separately from rate of responding (RR), thereby separating nociception from non-specific motor effects. Our very first paper, using this procedure was published in 1977 (Dykstra and McMillan, 1977).

Back to the Opioids

The time we took to perfect the procedure proved to be a very good investment. First, we took pains to show that the squirrel monkey titration procedure was sensitive to the effects of morphine-like analgesics, including morphine, methadone and meperidine. Second, we collected data to show that drugs without marked analgesic effects such as diazepam or chlorpromazine produced a profile distinct from that of morphine-like drugs. Third, subsequent studies showed that this procedure was sensitive to the antinociceptive effects of a range of mixed-action opioids. Moreover, many of the known pharmacological relationships that have been observed for opioids in other contexts were apparent as well, That is, morphine's effects could be antagonized by an opioid antagonist and tolerance to morphine's effects developed at a predictable rate.

In order to provide a closer look at some of our discoveries, let's look at a few of the questions we asked and answers we obtained during those early years. First, our earliest research established the fact that morphine produced dose-dependent increases in the level at which monkeys would maintain a nociceptive stimulus, and that it did so at doses that did not produce marked decreases in rate of responding. Second, morphine's profile was different from that of another interesting compound, buprenorphine, which produced a shallower dose-effect curve, spanning a more extended range of doses than morphine (Dykstra, 1985). Interestingly, these data were collected in the 1980s, following even earlier investigations of buprenorphine in rodents (Cowan et al., 1977). Given the recent successful introduction of buprenorphine as a viable treatment for opioid dependence, some 25 years after these initial observations, perhaps one can appreciate the time that often passes between initial observations in the laboratory and successful applications in clinical settings.

With clear evidence that morphine and other opioids presumed to act at the mu opioid receptor were active in the titration procedure, we went on to determine whether other types of opioids, namely kappa opioid agonists, would also reveal an antinociceptive profile in the titration procedure. In carrying out these studies, I was influenced by the sabbatical year I spent at the University of Michigan, with Jim Woods and Gail Winger and our shared interest in the mediation of opioid effects by acting through distinct opioid receptors, specifically the mu and kappa opioid receptor types.

In order to examine the differential effects of the opioids, our laboratory at Carolina returned to the squirrel monkey titration procedure. First, we established dose-effect curves for two prototypic mu agonists, l-methadone and fentanyl; then we did the same for two putative kappa agonists, U50,488 and bremazocine. Once replicable dose-effect curves were obtained, we redetermined each of these dose-effect curves in combination with the mu-selective opioid antagonist, quadazocine. And what we saw was that whereas it took only a very low dose of quadazocine (somewhere around 0.1 mg/kg) to produce a two-fold shift in the dose-effect curve for l-methadone and fentanyl, a noticeably higher dose (1.0 mg/kg) was required to produce a comparable shift in the kappa agonist dose effect curves. The pharmacological strength of these findings was confirmed with a pA2 analysis, in which we took all those data points, and crunched them up into just one value, the pA2 value, revealing that the dose of antagonist required to shift the kappa dose-effect curves was approximately one-log unit higher than the dose required to shift the mu dose-effect curve. Now those findings may seem pedestrian now, but at the time, we were very pleased to be able to show that the antinociceptive profile of kappa agonists, as observed in the monkey titration procedure, yielded the same pharmacological principles as had been observed in other in vitro contexts and allowed us to infer that the antinociceptive effects of kappa agonists were mediated through action at kappa opioid receptors (Dykstra and Massie, 1988).

We discovered other ways to reveal the complex pharmacology of the opioids and for this next phase of research, I am particularly indebted to a remarkable group of graduate students and colleagues. In a series of studies conducted by Kelly Powell, Rebecca Craft, Pam Doty and Mitch Picker, we were able to show that monkeys did develop tolerance to morphine in our procedures. Moreover, though morphine-tolerant monkeys revealed cross tolerance to other mu agonists, they were not cross tolerance to a range of kappa agonists (Doty, Picker and Dykstra, 1989; Craft and Dykstra, 1990).

In other studies, conducted by Alison Oliveto and Steve Negus, we were able to reveal the antagonist properties of a full range of opioids. Indeed, as we investigated buprenorphine's properties further, we were somewhat surprised to see that, in addition to its mu agonist profile, it also appeared to have kappa antagonist properties. (Oliveto and Dykstra, 1987; Negus and Dykstra, 1988)

Clearly none of these observations were made in a vacuum, but rather were the result of some very talented Psychology and Neurobiology graduate students, as well as several postdoctoral fellows. The accompanying figure provides a sample of some of those who worked in our laboratory throughout that time. The entire group included Margaret Healey, Richard Carter, Ray Genovese, Pam Doty, Jeffrey Witkin and later Alison Oliveto, Sandra Mattox, Rebecca Craft, Steve Negus, Kelly Powell as well as Mitch Picker, who was a thoughtful colleague throughout this period, while concurrently leading his own research program investigating the discriminative properties of opioid analgesics.

FIGURE 3: CAROLINA STUDENTS

Alison Oliveto, Sandra Mattox, Rebecca Craft

Kelly Powell

Pam Doty, Jeffrey Witkin,

Steve Negus

Mitch Picker

Opioids in Combination

Now, by this time, we had examined a number of candidate compounds that seemed to improve upon morphine's analgesic profile, drugs such as buprenorphine. The question then arose as to whether other types of opioid agonists, those with activity at the delta opioid receptor type, might have potential as analgesics, or as combinations with morphine to potentiate morphine's effects. What followed from that question was a series of promising studies indicating that the effects of mu agonists were increased in the presence of delta agonists (Dykstra et al., 1993; Dykstra 2002).

The pioneering findings from another laboratory (Trujillo and Akil, 1991) suggested that the development of morphine tolerance could be attenuated with an uncompetitive NMDA antagonist. New questions grew out of these findings and many of these captured the interests of a new group of colleagues, most notably, Ellen Walker, Ray Pitts, Chris Hughes, Art Granger and Rich Allen shown here in the accompanying figure.

FIGURE 4

Ellen Walker, Ray Pitts, Chris Hughes and Rich Allen

Given growing evidence that NMDA receptor complex modulates the effects of a number of drugs of abuse, including morphine, the obvious question became: By combining a mu opioid such as morphine with an NMDA antagonist, might it be possible to administer lower doses of morphine (thereby decreasing the risk of unwanted effects such as respiratory depression) and still obtain equivalent analgesia? And even more exciting, might it be possible to do this while decreasing the rate and/or extent to which tolerance might develop?

Rich Allen led the effort within our laboratory. First, he carefully examined a full range of doses of morphine in the titration procedure, sharpening the observation by analyzing morphine's effects over a clearly differentiated time line. Then, he redetermined morphine's effects in combination with a noncompetitive NMDA receptor antagonist (dextromethorphine) and subsequently with the competitive NMDA receptor antagonist, LY235959 and a glycine-site antagonist. With each experiment, he showed that morphine's effects were greater when administered in combination with an NMDA antagonist than when administered alone. Importantly, these increases in MSL occurred, without concomitant decreases in rate of responding, demonstrating that the enhancement was not due to non-specific motor effects. And interestingly, subsequent studies showed that the effects of other opioid agonists were also increased in the presence of an NMDA antagonist (Allen and Dykstra, 2001; Allen et al., 2002; 2003).

Recent Investigations in Mice:

As our investigators became more pharmacological, as squirrel monkeys became more difficult to obtain and as other opportunities became available—such as the possibility of posing relevant questions in genetically altered mice----we moved on. This change required another sabbatical year with Duke University colleagues Marc Caron, Laura Bohn, Amy Mohn and Raul Gainetdinov, who introduced me to the intricacies of working with mice, particularly those in which the NR1 subunit of the NMDA receptor had been knocked down.

Once back in Chapel Hill after a stimulating sabbatical, I was joined by yet another group of talented students and postdoctoral fellows. They included Kelly Carrigan, Laurence Miller, Brad Fischer, Jameeliyah Lane and Sara Ward.

Now, clever as a mouse might be, we did abandon the more complex titration procedure in this next series of studies, using traditional measures of antinociceptive, the hot plate and the tail flick procedures. But before embarking on studies in mice lacking function within the NMDA system, we wanted to determine whether the same NMDA antagonists that had altered the effects of morphine in the squirrel monkey titration procedure, also did so in a mouse model, using the hot plate procedure. We used C57Bl6J mice for these studies since they represent the predominant background strain for the NR1 knockdown mice, and what we learned was that a range of NMDA antagonists, each acting at different sites on the glutamate receptor complex, all increased morphine's antinociceptive effects in the hot place procedure, revealed by leftward shifts in the morphine dose-effect curve.

The next step was to determine whether there were parallel alterations in morphine's effects in mice in which the NR1 subunit of the NMDA receptor had been knocked down. And here the data got more interesting. But first, let me tell you a little about how we did these studies. All studies used mice in which the NR1 subunit of the NMDA receptor has been knocked down, yielding a depletion of approximately 5% as created by Mohn et al., 1999.

Experiments conducted by Brad Fischer using a cumulative dosing procedure to examine morphine's effects, indicated that the antinociceptive effects of morphine were attenuated in $NR1^{-/-}$ mice as compared to their WT controls. Clearly, additional experiments using larger numbers of mice, additional measures of antinociception, other testing parameters (i.e., other temperatures, regimens of administration), and perhaps additional NMDA antagonists are required in order to provide a consistent understanding of the role that NMDA plays in the antinociceptive effects of opioid agonists.

Closing Notes

This ends my summary of how our laboratory has combined both behavioral, pharmacological and more recently genetic approaches in order to better understanding the complex ways in which opioids alter behavior and how an

understanding of those mechanisms might be used to clinical advantage, whether it be for the treatment of pain, or as a potential intervention in treating drug dependence

In bringing these data together, I set out to emphasize not only the findings, but the context in which they were obtained, namely, through multiple collaborations, helpful colleagues and a mountain of dissertation projects. By emphasizing this context of collegiality, it has been my intention to honor Marian Fischman's enduring legacy as a mentor and a colleague.

In closing, I also want to acknowledge

- the University of North Carolina at Chapel Hill, for providing not only the physical facilities that made this work possible, but also the programs that drew the students and faculty colleagues to our laboratory.
- NIDA for providing continuous support to our laboratory over the last 30 years, through numerous research grants, research scientist awards and training grants.
- CPDD for providing the forum in which much of our research was shared and for its visible support of mentorship and collegiality.
- My family, especially my husband Bill, who only wishes he could attend more CPDD meetings and
- Many, many mentors and friends--those who provided encouragement and advice as well as those who questioned, corrected and inspired--all done in the tradition that the namesake of this award, Marian Fischman, so beautifully conveyed.

Colleague, Mentor and Friend

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AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2006)

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THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates a variety of compounds with CNS activity for preclinical physical dependence potential and abuse liability as a public health service. DEC works with researchers from academia, industry, and also governmental organizations (FDA, DEA, NIDA, WHO) to characterize the pharmacological profile of compounds in order to facilitate decisions on matters ranging from medication development to drug scheduling. The duties of the Biological Coordinator of DEC (Dr. A. Coop) involve receiving samples for evaluation and distributing them blind to the relevant pharmacological groups within DEC. All data are collated by the Biological Coordinator, who maintains a confidential database and corresponds with the submitters. The Biological Coordinator also maintains the DEC website (http://www.cpdd.vcu.edu/DEC_ARCHIVES/dec.pdf) which contains archived DEC annual reports and the DEC indices (http://www.pharmacy.umaryland.edu/faculty/acoop/dec%20folder/DEC%20indices2003web.xls), a list of all compounds evaluated by DEC and reference to their year of publication. In order to improve access to information, the Biological Coordinator is currently updating the indices with the goal of including links to original data in the on-line DEC annual reports. The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley, C. Cook) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor, H. Ko), and four stimulant/depressant testing groups, at the University of Mississippi Medical Center (UMMC, Dr. W. Woolverton), University of Texas Health Science Center at San Antonio (UTHSCSA, Drs. C. France, L. McMahon), University of Michigan (UM, Drs. G. Winger, J. Woods), and Yerkes National Primate Research Center, Emory University (Dr. W. Fantegrossi). Drs. T. Cicero and A. Jacobson are emeritus members.

DEC reports to the CPDD Committee on Abuse Liability Testing (CALT; formerly the DEC Liaison Committee; Dr. S. Negus, Chair). Members of both that CPDD committee and other CPDD committees, as well as representatives from governmental agencies, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Michigan in May 2006 to discuss the work which has been accomplished and future plans. Separate meetings are held at VCU with the members of the VCU Analgesic Testing Group, as well as Drs. E. May and E. Bowman, Dr. A. Coop, and a NIDA representative (Dr. D. McCann), to discuss the results obtained from the VCU testing and research program.

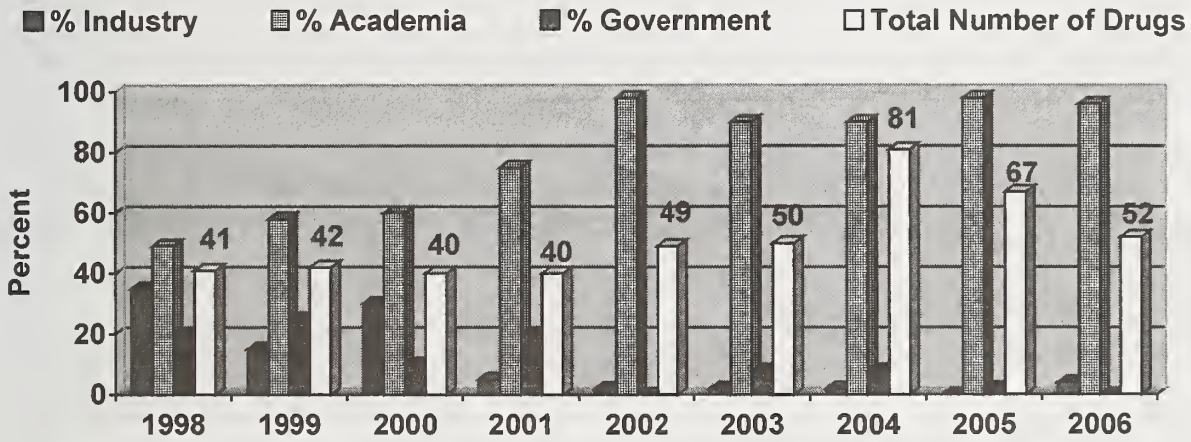
This report provides an overview of the results obtained by all groups within DEC; precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2007; Traynor and Woods, 2007). Data obtained under the auspices of DEC are held confidential for a maximum of three years, but can be released prior to the three-year limit with the permission of the submitter. Data were released for publication this year on 52 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure remains high by historical standards, but has dropped from recent unusually high numbers. Of these 52 compounds, 35 were evaluated at VCU (antinociceptive assays in mice: tail flick, hot plate, and phenylquinone antiwrithing, and the tail-flick antagonist assay; as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys and rats), and 43 at UM (binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies). Compounds were submitted primarily from academia; two compounds came from industrial submitters. Figure 1 shows the continuing trend that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from other sources decreasing. Several new pharmaceutical companies have submitted a large number of compounds over the past 2-3 years, thereby increasing the diversity of sources for compounds to be released starting in 2007. No compounds were released from the Stimulant/Depressant program this year.

Four publications based on the data gathered under DEC auspices were published since the last annual report (Fantegrossi *et al.*, (2005); Fantegrossi *et al.*, (2006); Harding *et al.*, (2005); Spetea *et al.*, (2005)).

EXPERIMENTAL OBSERVATIONS

Compounds released for publication this year are listed in Table 1; their molecular structures and a summary of their *in vivo* and *in vitro* data are in Tables 2 to 10. As in previous years (Coop, 2006), the compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Table 2; phenylmorphans and neodihydrothebaines in Table 3; 6,7-benzomorphans in Tables 4-7; small amines in Table 8; natural products in Table 9; cannabinoids in Table 10. Numerous interesting compounds were released this year, and they are discussed below. For compounds that have been evaluated previously, the new data are discussed in relation to the published data.

FIGURE 1. DEC TESTING PROGRAMS: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1998-2006)



As reported previously (Coop, 2005, 2006), the 14-phenylpropyloxy morphinans represent a unique class of opioids with extraordinary potency as antinociceptive agents (10,000 x morphine), and high affinity for all three opioid receptors (Greiner *et al.*, 2003, Spetea *et al.*, 2004). One member of this class, **NIH 11056** (Table 2) was evaluated for its duration of antinociceptive action in the tail flick assay. An extended duration of action was noted (15 hours), raising the possibility of development into a long duration analgesic or pharmacotherapy for opiate dependence.

NIH 11198 (Table 2) is an ester prodrug of oxycodone (NIH 11107, Coop, 2003). The affinity of NIH 11198 for mu receptors is 2-3-fold lower than oxycodone (K_i = 1200 nM vs. 485 nM for oxycodone). In GTPγS functional assays, this compound was shown to be a full mu agonist, albeit of very low potency. Thus, there appears little difference between the *in vitro* profiles of oxycodone and NIH 11107.

The phenylmorphans, **NIH 8508** and **NIH 8509** (Table 3) have previously been shown to possess antinociceptive activity (Jacobson, 1981). The two isomers were evaluated in order to determine the receptor through which the activity is derived: NIH 8509 was reversed with β-FNA indicating mu agonist activity, whereas NIH 8508 could not be reversed by any of the selective antagonists. Further studies on NIH 8508 are warranted to determine the origin of its antinociceptive activity. **NIH 11261**, **NIH 11262**, and **NIH 11263** (Table 3) are (+)-neodihydrothebaine, (+)-bractazonine, and a substituted (+)-bractazonine, respectively. Novel syntheses of these compounds were reported recently (Chen et al., 2005), allowing evaluation showing no opioid activity.

Table 4 contains (-)-N-alkyl and N-alkynyl benzomorphans as a continuation of our previous studies to determine the effects of N-substituents in this series (May *et al.*, 2003; May *et al.*, 1998). The N-alkynyl derivatives (**NIH 11254**, **NIH 11256**, and **NIH 11258**) show high affinity at opioid receptors, weak antinociceptive activity, but potent morphine antagonism. This suggests that the compounds are mu antagonists and kappa agonists, but further sub-type testing is required to confirm such a profile. The corresponding (+)-isomers are shown in Table 5 and, as expected, show lower affinity for opioid receptors. Unexpectedly, **NIH 11255** shows increased morphine

antagonist potency than its corresponding (-)-isomer (**NIH 11256**). Tables 6 and 7 show benzomorphan isomers with ether N-substituents. The phenoxyethyl derivatives ((-) **NIH 11236** and (+) **NIH 11237**) show moderate to good binding affinity, but are noteworthy due to their inverse agonism at kappa receptors. Both isomers reduce basal activity in the GTPγS assays by about 40%, and represent excellent lead compounds for the development of high affinity inverse kappa agonists.

The tertiary amines (**NIH 11169** to **NIH 11171**) in Table 8 are phenylethylamines which can be superimposed on the morphinan skeleton. Surprisingly for such simple achiral compounds, moderate affinity for opioid receptors is seen, with **NIH 11169** showing excellent affinity and selectivity for kappa receptors. The substituted piperidine (**NIH 11273**) and piperazines (**NIH 11274** and **NIH 11275**) in Table 8 were assayed for their opioid binding affinity for similar reasons. All compounds showed low affinity.

Salvinorin A (NIH 11228) has been reported as a naturally occurring non-nitrogenous kappa opioid agonist with hallucinogenic activity (Harding *et al.*, 2005, Coop, 2006). An analysis of structurally similar compounds isolated from common sage (**NIH 11297-11303**, Table 9) indicated no binding affinity to opioid receptors. Such analyses aid in delineating the structural requirements for binding to kappa opioid receptors, with the aim of understanding ligand-receptor complexes at the molecular level.

The two cannabinoid agonists CP 55940 (**NIH 11276**) and Win 55,212-2 (**NIH 11277**) are shown in Table 10. These studies show that the mouse antiwrithing assay is useful for evaluating CB1 agonists as antinociceptive agents, and that the effects of CB1 agonism can be effectively reversed by a selective CB1 antagonist, but are unaffected by a CB2 antagonist.

TABLE 1. COMPOUNDS EVALUATED

	COMPOUND NAME	TABLE #-Evaluator
NIH#	**ANALGESIC TESTING PROGRAM**	
8508	(-)-5-(*m*-Hydroxyphenyl)-2-methylmorphan.HCl	3-VCU
8509	(+)-5-(*m*-Hydroxyphenyl)-2-methylmorphan.HCl	3-VCU
11056	17-Cyclopropylmethyl-4,5α-epoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU
11169	*N*-[(3-Hydroxy)-2-phenethyl]-*N*-cyclobutylmethyl-2-phenylethylamine.HCl	8-UM
11170	*N*-[(3-Hydroxy)-2-phenethyl]-*N*-cyclopropylmethyl-2-phenylethylamine.HCl	8-UM
11171	*N*-[(4-Hydroxy)-2-phenethyl]-*N*-cyclopropylmethyl-2-phenylethylamine.HCl	8-UM
11184	5,6-Didehydro-3,4,14β-trimethoxy-17-methylmorphinan-6-carboxamide	2-VCU/UM
11193	Substance P-opioid hybrid	2-VCU/UM
11198	2-(Benzyloxycarbonylamino)dl-pentanedioic acid-1-(3-methoxy-14-hydroxy-6,7-disehydro-4,5α-epoxy-17-methylmorpinan-6-yl)ester	2-UM
11231	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	5-VCU
11232	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	4-VCU
11233	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	7-VCU
11234	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	6-VCU
11236	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxyethyl)-6,7-benzomorphan.HCl	6-VCU/UM

TABLE 1. COMPOUNDS EVALUATED (continued)

11237	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxyethyl)-6,7-benzomorphan.HCl	7-VCU/UM
11249	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr	5-VCU/UM
11250	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr	4-VCU/UM
11253	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan.HCl	5-VCU/UM
11254	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan.HCl	4-VCU/UM
11255	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate	5-VCU/UM
11256	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate	4-VCU/UM
11257	(+)-(1S,5S,9S)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	5-VCU/UM
11258	(-)-(1R,5R,9R)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	4-VCU/UM
11259	(+)-(1S,5S,9S)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	5-VCU/UM
11260	(-)-(1R,5R,9R)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	4-VCU/UM
11261	(+)-Neodihydrothebaine.HCl	3-VCU/UM
11262	(+)-Bractazonine.HCl	3-VCU/UM
11263	(+)-(3-Oxobutyl)bractazonine.HCl	3-VCU/UM
11265	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan.HCl	5-VCU/UM
11266	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan.oxalate	4-VCU/UM
11267	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan.oxalate	5-UM
11268	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan.oxalate	4-UM
11269	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan.oxalate	5-VCU/UM
11270	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan.HCl	4-VCU/UM
11271	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan.HCl	5-UM
11272	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan.HCl	4-VCU/UM
11273	3-Methyl-1-(3-phenylpropyl)piperidine.oxalate	8-VCU/UM
11274	1-(2-phenethyl)-4-(2-pyridyl)piperazine.oxalate	8-UM
11275	1-(3-Phenylpropyl)-4-(2-pyridyl)piperazine.oxalate	8-VCU/UM
11276	(1R,3R,4R)-3-[2Hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)-cyclohexan-1-ol	10-VCU
11277	(R)-(+)-[2,3-Dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl](1-napthalenyl)methanone	10-VCU

TABLE 1. COMPOUNDS EVALUATED (continued)

11285	(+)-(1S,5S,9S)-2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11286	(-)-(1R,5R,9R)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-VCU/UM
11287	(+)-(1S,5S,9S)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate	7-VCU/UM
11288	(-)-(1R,5R,9R)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate	6-UM
11297	Compound for Sage	9-UM
11298	Compound for Sage	9-UM
11299	Compound for Sage	9-UM
11300	Compound for Sage	9-UM
11301	Compound for Sage	9-UM
11302	Compound for Sage	9-UM
11303	Compound for Sage	9-UM

NOTES FOR TABLES 2 – 10

Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2007; Traynor and Woods, 2007). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained at 30 mg/kg. NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist administered i.c.v as μg/brain).

1) Antinociceptive reference data:

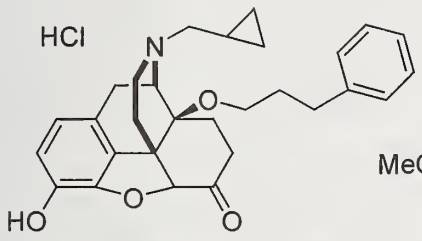
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone antiwrithing = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

2) *In Vitro*:

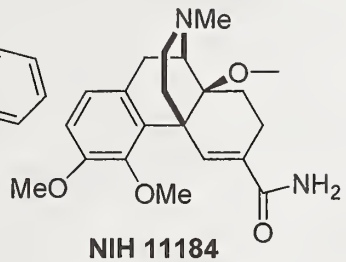
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-diprenorphine. K_i values for standard ligands: μ (DAMGO 7.6 nM, morphine 11.2 nM); δ (SNC80 0.8 nM); κ (U69593 0.3 nM). [^{35}S]GTPγS functional data were obtained with the recombinant receptors described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved: μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM (100% stimulation); δ (ED_{50}) SNC80 = 9 nM (100% stimulation), DPDPE = 8.3 nM (60% stimulation); κ (ED_{50}) U69,593 = 31 nM (100% stimulation), bremazocine = 0.5 nM (86% stimulation).

References to previous Drug Evaluation Committee annual reports are shown in parentheses, and refer to the year of publication.

TABLE 2. 4.5-EPOXYMORPHINANS AND MORPHINANS



NIH 11056



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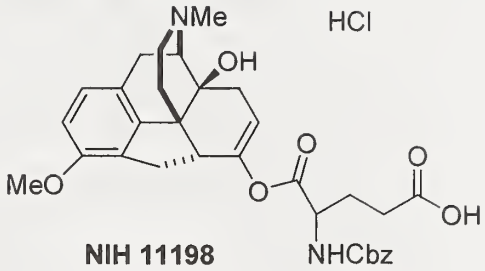


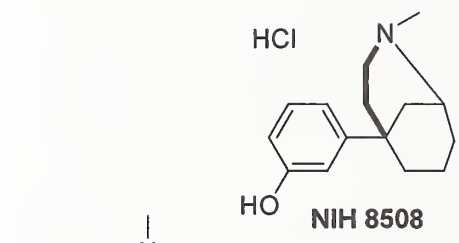
NIH 11198

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (EC_{50}, nM and % stimulation)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11056[a]	0.0023[a]	0.0062[a]	0.0032[a] Duration of action: 15 hours[b]	Inactive[a]	μ=0.06, δ=0.38, κ=0.11[a]	Substitution for morphine at 0.04[a]
11184	Inactive	0.18	Inactive	Inactive	μ=6.1, δ=96, κ=300	-
11193	Inactive	Inactive	Inactive	Inactive	μ=80, δ=300, κ=970	Neither substituted for morphine nor exacerbated withdrawal at 2.5 and 10
11198	-	-	-	-	μ=1200, δ=420, κ> 10,000 GTPγS: μ EC_{50}=3800, 96% stimulation; δ 0% stimulation	-

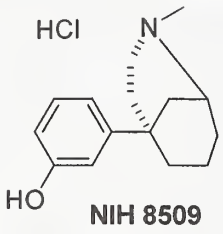
a) Previously reported (Coop, 2005)

b) New data.

TABLE 3. PHENYLMORPHANS AND NEODIHYDROTHEBAINES



NIH 8508



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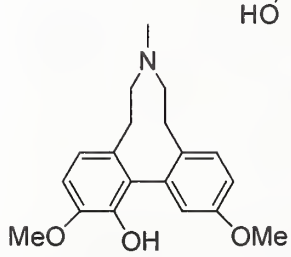
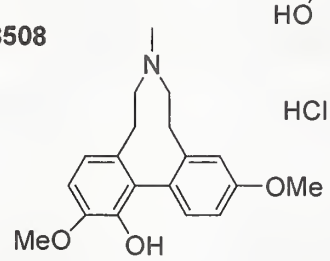
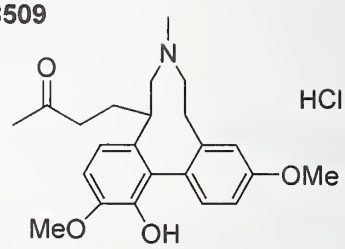


NIH 11261



NIH 11262

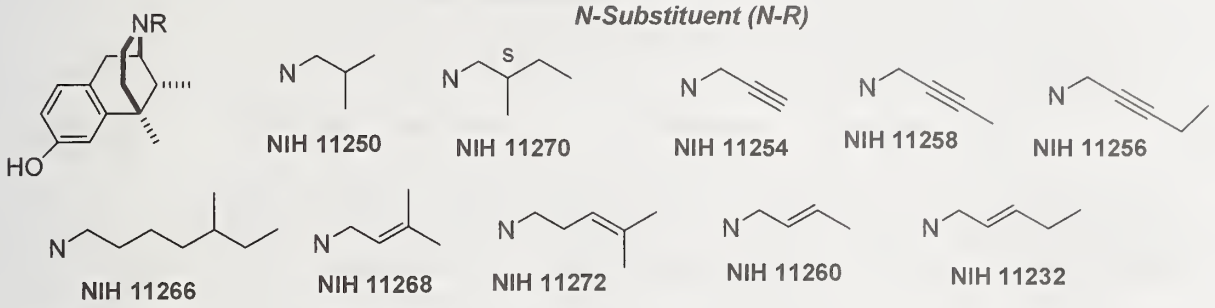


NIH 11263

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenyl-quinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
8508[a]	1.7[a] Antagonism by selective antagonists: norBNI, NTI, β-FNA: Inactive	-	-	-	-	Partial suppression of withdrawal signs at 5; inactive at 10.
8509	0.35	0.5	4.8 Antagonism by selective antagonists: norBNI, NTI: Inactive β-FNA: AD_{50}=0.28	Inactive	-	Dose related suppression of withdrawal signs
11261	Inactive	4.6	Inactive	Inactive	μ, δ, κ>10,000	-
11262	Inactive	Inactive	Inactive	Inactive	μ=5300, δ>10,000, κ=5300	-
11263	Inactive	Inactive	Inactive	Inactive	μ=1800, δ=1700, κ>10,000	-

a) Previously published (1981)

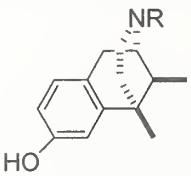
TABLE 4. (-)-*N*-ALKYL-BENZOMORPHANS



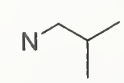
	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11232	Inactive[a]	0.74[a] Antagonism of ED_{80}: NTI - Inactive[b]	Inactive[a]	Inactive[a]	μ=4.1, δ=130, κ=7.2[a]	-
11250	Inactive	0.83	Inactive	Inactive	μ=2.8, δ=29, κ=0.9	Dose related attenuation of withdrawal signs at 0.05 and 0.2. Slowing and ataxia noted.
11254	Inactive	2.1	Inactive	0.18	μ=2.1, δ=4.5, κ=0.8	Precipitated withdrawal at 1 and 4
11256	Inactive	0.57	Inactive	4.7	μ=2.1, δ=130, κ=3.6	-
11258	Inactive	0.21	Inactive	0.65	μ=1.9, δ=39, κ=2.0	-
11260	Inactive	Inactive	Inactive	0.32	μ=3.2, δ=29, κ=2.2	Precipitated withdrawal at 1 and 4
11266	Inactive	6.3	24	Inactive	μ=4.0, δ=42, κ=26	Neither attenuated nor exacerbated withdrawal at 4.5 and 18.
11268	-	-	-	-	μ=5.6, δ=110, κ=13	-
11270	-	-	-	-	μ=5.3, δ=22, κ=2.8	-
11272	-	-	-	-	μ=0.97, δ=6.0, κ=6.6	-

a) Previously published (Coop, 2006)
b) New data

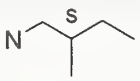
TABLE 5. (+)-N-ALKYL-BENZOMORPHANS



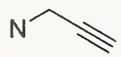
N-Substituent (N-R)



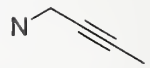
NIH 11249



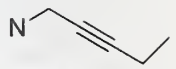
NIH 11271



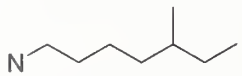
NIH 11253



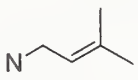
NIH 11257



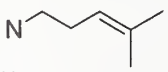
NIH 11255



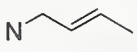
NIH 11267



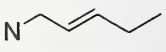
NIH 11269



NIH 11265



NIH 11259

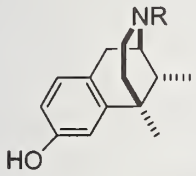


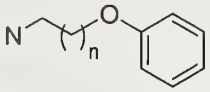
NIH 11231

	MOUSE ANTINOCICEPTIVE ASSAYS			*IN VITRO*	MONKEY	
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11231	Inactive	1.6	Inactive	Inactive	μ=240, δ=3100, κ=89	Neither attenuated nor exacerbated withdrawal at 2.5 and 10.
11249	Inactive	Inactive	Inactive	Inactive	μ, δ>10,000, κ=83	-
11253	Inactive	6.7	Inactive	8.9	μ=500, δ=1500, κ=160	-
11255	Inactive	Inactive	Inactive	1.7	μ=250, δ=3300, κ=70	-
11257	Inactive	Inactive	Inactive	13	μ=270, δ=4000, κ=98	-
11259	Inactive	Inactive	Inactive	Inactive	μ=210, δ=6100, κ=120	-
11265	-	-	-	-	μ=130, δ=1000, κ=270	-
11267	-	-	-	-	μ=310, δ=2900, κ=94	-
11269	Inactive	Inactive	Inactive	Inactive	μ=310, δ=4600, κ=65	-
11271	-	-	-	-	μ=560, δ=2900, κ=48	-

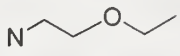
TABLE 6. (-)-N-ALKOXY-BENZOMORPHANS

N-Substituent (N-R)

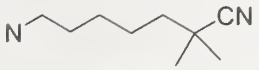




NIH 11234 n=2
NIH 11236 n=1



NIH 11288

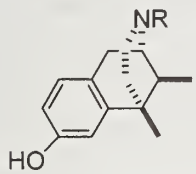


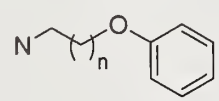
NIH 11286

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation and EC_{50}, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11234	0.64	0.42	2.1	Inactive	μ=1.2, δ=5.2, κ=10	Substitution for morphine at 2.5; convulsions at 10.
11236	-	4.8	9.6	-	μ=10, δ=92, κ=75 GTPγS: μ 28% stimulation; δ <5% stimulation; κ -41% of basal (EC_{50}=775)	Attenuated withdrawal signs at 10.
11286	-	-	-	-	μ=9.4, δ=39, κ=77	-
11288	-	-	-	-	μ=1.2, δ=30, κ=2.0	-

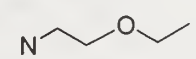
TABLE 7. (+)-N-ALKOXY-BENZOMORPHANS

N-Substituent (N-R)

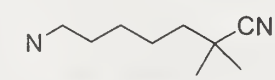




NIH 11233 n=2
NIH 11237 n=1



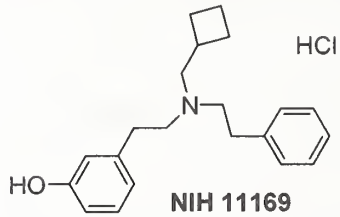
NIH 11287



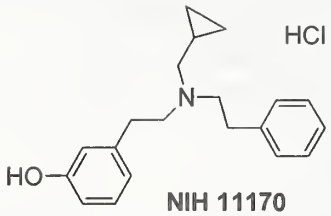
NIH 11285

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation and EC_{50}, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11233	Inactive	2.8	Inactive	Inactive	μ=77, δ=3100, κ=600	Complete substitution for morphine at 2 and 10.
11237	14	6.8	Inactive	Inactive	μ=85, δ=2100, κ=110 GTPγS: μ <5% stimulation; κ -40% of basal (EC_{50}=300)	Neither substituted for morphine nor exacerbated withdrawal at 10
11285	-	-	-	-	μ=380, δ=3100, κ=530	-
11287	-	-	-	-	μ=2.1, δ=2600, κ=220	-

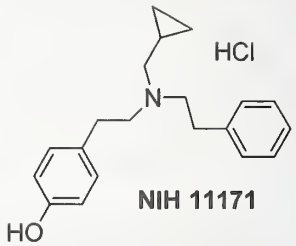
TABLE 8. SMALL AMINES



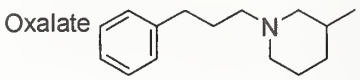
NIH 11169



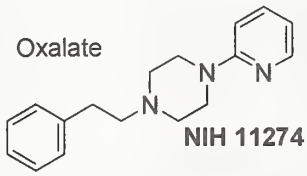
NIH 11170



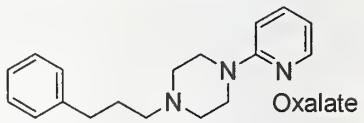
NIH 11171



NIH 11273



NIH 11274

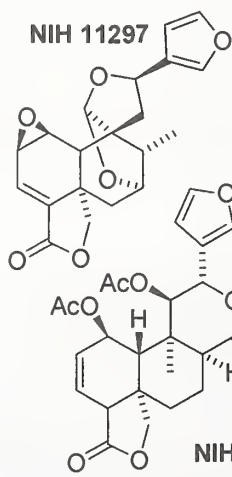


NIH 11275

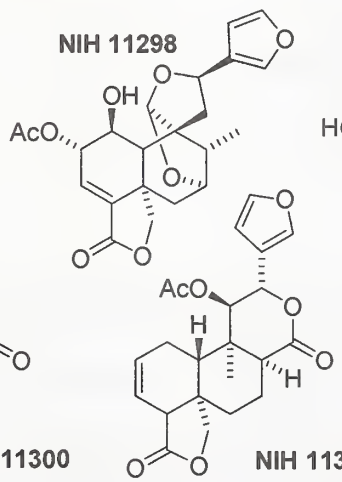
IN VITRO

NIH #	Binding Affinity, (K_i, nM)
11169	μ=85, δ=620, κ=3.4
11170	μ=170, δ=1500, κ=60
11171	μ=100, δ=930, κ=300
11273	μ, κ, δ >10,000
11274	μ=1100, δ, κ >10,000
11275	μ=450, δ > 10,000, κ=6000

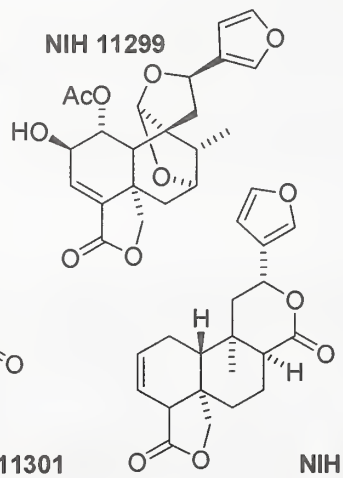
TABLE 9. NATURAL PRODUCTS



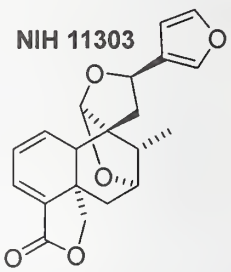
NIH 11297



NIH 11298



NIH 11299



NIH 11303

NIH 11300

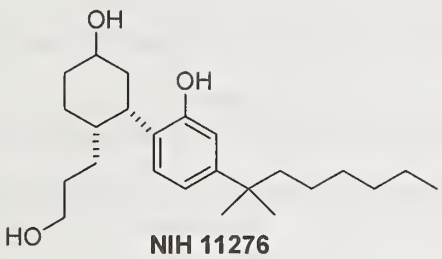
NIH 11301

NIH 11302

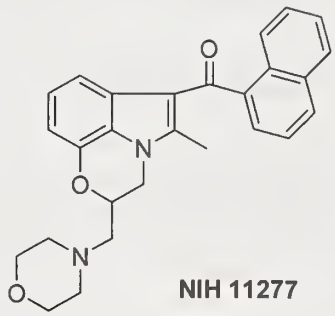
IN VITRO

NIH #	Binding Affinity, (K_i, nM)
11297	μ, δ, κ >10,000
11298	μ, δ, κ >10,000
11299	μ, δ, κ >10,000
11300	μ, δ, κ >10,000
11301	μ, δ, κ >10,000
11302	μ, δ, κ >10,000
11303	μ, δ, κ >10,000

TABLE 10. CANNABINOIDS



NIH 11276



NIH 11277

MOUSE ANTINOCICEPTIVE ASSAYS

NIH #	Phenylquinone (ED_{50}, s.c., mg/kg)	Antagonism of PPQ ED_{80} with SR 141716A (CB1) (AD_{50}, s.c., mg/kg)	Antagonism of PPQ ED_{80} with SR 144528 (CB2) (AD_{50}, s.c., mg/kg)
11276	0.0095	1.04	Inactive at 1 and 10
11277	0.17	0.1	Inactive at 1 and 10

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ACKNOWLEDGEMENT

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DRUG EVALUATION COMMITTEE REPORT ON: EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2006)

John R. Traynor and James H. Woods

Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor, MI

This report contains information on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained usually involves *in vitro* evaluation for opioid activity. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is currently administered by the Biological Coordinator, Dr. A. Coop, University of Maryland. The compounds come originally from pharmaceutical companies, universities, government laboratories, or international organizations.

At the UM and MCV laboratories, drug samples arrive from the Biological Coordinator with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information. After the evaluation is complete and the report sent to Dr. Coop, the submitter of the compound(s) is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter can withhold the structure for up to three years. When the structure is released all of the data on the compound are reported herein.

SUMMARY OF TESTS PERFORMED

The compounds that were evaluated at the University of Michigan and available for release during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator.

NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator
11169	17 March 2003	11265	20 October 2005
11170	17 March 2003	11266	20 October 2005
11171	17 March 2003	11267	20 October 2005
11184	16 September 223	11268	20 October 2005
11193	21 November 2003	11269	20 October 2005
11198	21 November 2003	11270	20 October 2005
11236	3 January 2005	11271	20 October 2005
11237	8 March 2005	11272	20 October 2005
11249	8 March 2005	11273	27 November 2005
11250	8 March 2005	11274	27 November 2005
11253	16 August 2005	11275	27 November 2005
11254	18 August 2005	11285	27 November 2005
11255	16 August 2005	11286	27 November 2005
11256	16 August 2005	11287	27 November 2005
11257	16 August 2005	11288	27 November 2005
11258	16 August 2005	11297	29 November 2005
11259	16 August 2005	11298	29 November 2005
11260	18 August 2005	11299	29 November 2005
11261	16 August 2005	11300	29 November 2005
11262	16 August 2005	11301	29 November 2005
11263	20 October 2005	11302	29 November 2005
11264	20 October 2005	11303	29 November 2005

SUMMARY OF FINDINGS

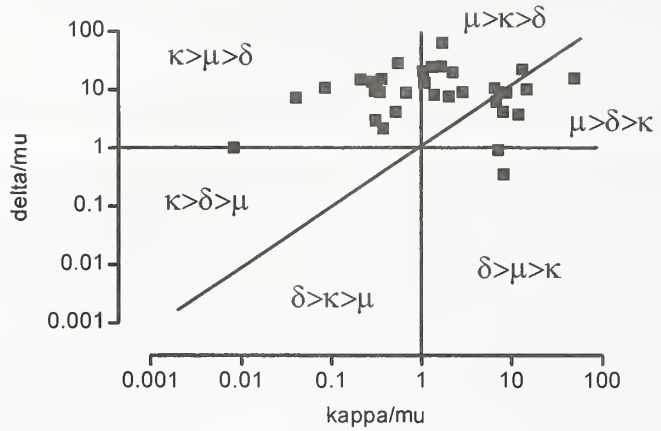


Figure 1. Distribution of selectivity of evaluated compounds with opioid receptor affinity (34 out of 44 compounds).

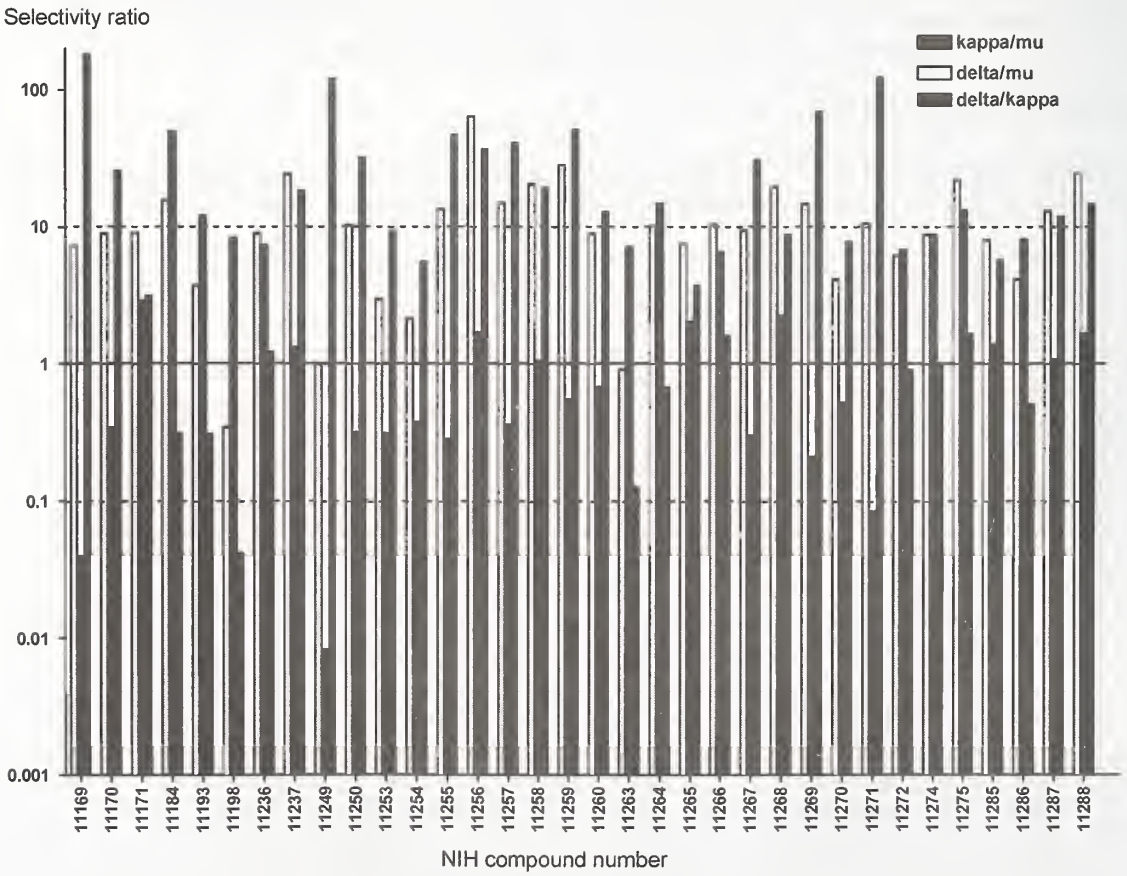


Figure 2. Opioid receptor selectivities of the 34 compounds with opioid receptor affinity. Compounds above the solid line have preference for mu receptors over kappa receptors, or delta receptors, or for kappa receptors over delta receptors. Compounds below the solid line have preference for kappa receptors, or delta receptors , over mu receptors or for delta receptors over mu receptors. Above and below the dotted lines indicates a selectivity of > 10 fold.

METHODS

Opioid Receptor Binding and In Vitro Efficacy Assessment

Details of the binding assay have been described previously (Lee *et al.,* 1999). Briefly, aliquots of a membrane preparation are incubated with [^{3}H]diprenorphine (0.3 nM) in the presence of different concentrations of the drug under investigation at 25° C for 1 hr. Specific, *i.e.*, opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10μM naloxone. The potency of the drugs in displacing the specific binding of [^{3}H]-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted to Ki values by the method of Cheng and Prussoff (1973). Opioid binding is performed in membranes from C_6 rat glioma cells expressing recombinant μ (rat; Emmerson et al., 1994) or δ (rat; Clark et al., 1997) and CHO cells expressing the recombinant κ (human, Zhu et al., 1997). The affinity (Kd) values of [^{3}H]diprenorphine at the receptors are: μ (0.15 nM); δ (0.45 nM); κ (0.25 nM).

The results of the selective binding assays are given as means ± SEM from three separate experiments, each performed in duplicate. Ki values for standard compounds using recombinant receptors and [^{3}H]diprenorphine as radioligand are: μ (DAMGO, 7.6 nM; morphine, 11.2 nM), δ (SNC80, 0.8 nM) and κ (U69593, 0.3 nM). If less than 50% displacement of [^{3}H]diprenorphine is seen at 10 μM, it is reported as > 10 μM and the percent displacement given in parentheses.

[^{35}S]GTPγS assays are carried out using membranes from C6 cells expressing either μ (Emmerson et al., 1996) or δ (Clark et al., 1997) receptors or CHO cells expressing κ receptors (Zhu et al., 1997). Assays are performed as described by Traynor and Nahorski (1995). Values are given as EC_{50} with % effect compared to a standard agonist (DAMGO, SNC80, or U69593) or as maximal stimulation achieved at 10 μM concentration. EC_{50} values (nM) for standard compounds are as follows: μ receptor (morphine, 65 nM; DAMGO, 34 nM; fentanyl, 13 nM), δ receptor (SNC80, 9 nM; DPDPE 8.3 nM), and κ receptor (U69593, 31.0 nM; bremazocine, 0.5 nM)

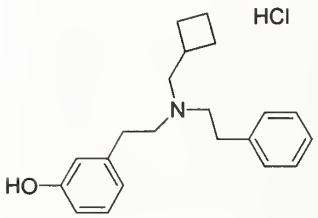
DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standards SNC80 and U69593. Morphine and DAMGO give equivalent responses.

Antagonist activity is given as AD_{50} values or as pK_B values. AD_{50} refers to the concentration of test compound that reduces [^{35}S]GTPγS binding stimulated by an ED_{80} concentration of appropriate agonist (DAMGO,μ; DPDPE,δ; U69593,κ) by 50%. pK_B is the concentration of antagonist required to shift the dose-effect curve for appropriate agonist by 2-fold. It is a measure of the affinity of the antagonist for a receptor.

Behavioral Assessments in Rhesus Monkeys.

No compounds assessed in rhesus monkeys were made available for release this year. A description of the assays available to submitters is included in the appendix.

NIH 11169 ***N*-Cyclobutylmethyl-*N*-[(3-hydroxy)-2-phenethyl]-2-phenylethylamine.HCl**



OPIOID RECEPTOR BINDING (nM)

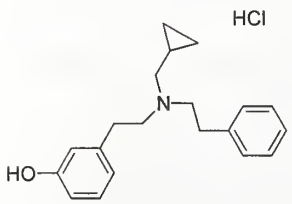
μ-receptor: 84.6 ± 12.5
δ-receptor: 616 ± 81
κ-receptor: 3.4 ± 0.8

SUMMARY

NIH 11169 has high affinity for the κ opioid receptor. It has 25-fold selectivity for the κ over the μ receptor and 180-fold selectivity over the δ receptor.

* * *

NIH 11170 ***N*-Cyclopropylmethyl-*N*-[(3-hydroxy)-2-phenethyl]-2-phenylethylamine.HCl**



OPIOID RECEPTOR BINDING (nM)

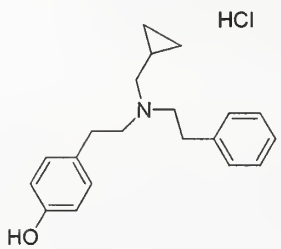
μ-receptor: 170 ± 6.1
δ-receptor: 1531 ± 417
κ-receptor: 59.2 ± 11.4

SUMMARY

NIH 11170 has affinity for the κ ≥ μ opioid receptor, and is 26-fold selective for κ over δ receptors.

* * *

NIH 11171 ***N*-Cyclopropylmethyl-*N*-[(4-hydroxy)-2-phenethyl]- 2-phenylethylamine.HCl**



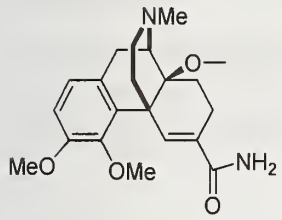
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 103 ± 25.9
δ-receptor: 933 ± 466
κ-receptor: 297 ± 78.1

SUMMARY

NIH 11171 has affinity for the μ ≥ κ opioid receptor and with less than 10-fold μ/δ selectivity.

NIH 11184 **5,6-Didehydro-3,4,14-tromethoxy-17-methylmorphinan-6-carboxamide**



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 6.1 ± 0.8
δ-receptor: 96.0 ± 3.6
κ-receptor: 304 ± 17.1

SUMMARY

NIH 11184 has high affinity for μ opioid receptors with 16-fold selectivity for μ over δ and 50-fold selectivity for μ over κ receptors.

* * *

NIH 11193 **(5α,6α)-7,8-Didehydro-4,5-epoxy-17-methyl(4α)-1,3,4,9,10,10a-α-hexhydro[2H]-10α,4α-(imnoethano)phenanthrene-3-ol, 6-(1,4-dioxo)-butanediyl-3-[α-*N*-acetyl, ε-imino-(lysyl)]-des-1-arginyl, des-2-prolyl-substance P**

OPIOID RECEPTOR BINDING (nM)

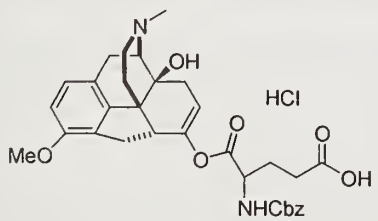
μ-receptor: 80.1 ± 10.7
δ-receptor: 298 ± 67
κ-receptor: 969 ± 178

SUMMARY

NIH 11193 has affinity for μ receptors and low to very low affinity for δ > κ opioid receptors.

* * *

NIH 11198 **2-(Benzyloxycarbonylamino)dl-pentanedioic acid-1-(3-methoxy-14-hydroxy-6,7-disehydro-4,5α-epoxy-17-methylmorpinan-6-yl)ester.HCl**



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1208 ± 4.6
δ-receptor: 419 ± 109
κ-receptor: 19 ± 1.5% inhibition at 10 μM

[^{35}S]GTPγS ASSAY

μ-receptor: 96.2 ± 4.9 % of max. stim.; EC_{50} = 3755 ± 285 nM
δ-receptor: <10% of maximal stimulation
κ-receptor: not done due to insignificant binding affinity

NIH 11198 (continued)

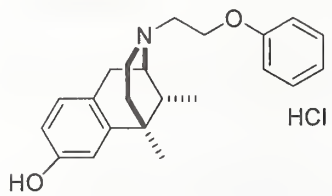
SUMMARY

NIH 11198 has low affinity for the δ receptor, with little selectivity over μ (3-fold), but no affinity for the κ receptor. It is a full μ agonist.

Note: These studies were performed in phosphate buffered solutions (pH 7.4), and were performed in parallel with studies on oxycodone (NIH 11107), as requested by the submitter.

* * *

NIH 11236 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-phenoxyethyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 10.3 ± 0.7
δ-receptor: 92.3 ± 15.3
κ-receptor: 75.4 ± 26.3

[^{35}S]GTPγS ASSAY

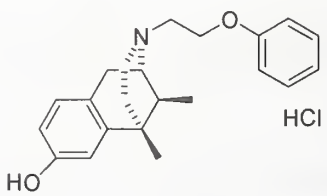
μ-receptor: 28 ± 7% of maximal stimulation; EC_{50} not available
δ-receptor: <5% of maximal stimulation
κ-receptor: -41 ± 4% of basal stimulation; EC_{50} = 775 ± 211 nM

SUMMARY

NIH 11236 has high affinity for the μ-opioid receptor, with 9-fold selectivity over δ and 7-fold selectivity over κ It is a weak partial agonist at the μ opioid receptor, is a low potency agonist at the κ opioid receptor, and had no measurable effect at the δ receptor.

* * *

NIH 11237 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-phenoxyethyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 84.6 ± 31.2
δ-receptor: 2060 ± 280
κ-receptor: 111 ± 28

[^{35}S]GTPγS ASSAY

μ-receptor: <5 % of maximal stimulation at 10 μM
δ-receptor: not done due to very low binding affinity
κ-receptor: -40 ± 7% of basal stimulation: EC_{50} = 300 ± 150 nM

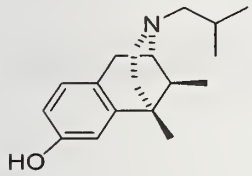
NIH 11237 (continued)

SUMMARY

NIH 11237 is an antagonist at the μ opioid receptor in C6μ cells but is a low potency agonist at the human κ opioid receptor expressing in CHO cells. In the binding assay, it had similar affinity for μ and κ opioid receptors and is 18-to 20-fold selective for these receptor over the δ receptor.

* * *

NIH 11249 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr



HBr

OPIOID RECEPTOR BINDING (nM)

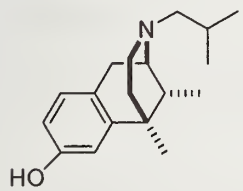
μ-receptor: 40 ± 3% inhibition at 10 μM
δ-receptor: 22 ± 5% inhibition at 10 μM
κ-receptor: 83 ± 31

SUMMARY

NIH 11249 has affinity for the κ-opioid receptor and has >100-fold selectivity for the κ opioid receptor over μ and δ opioid receptors.

* * *

NIH 11250 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr



HBr

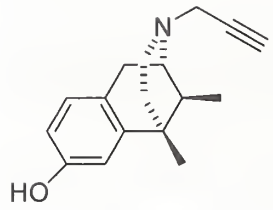
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2.8 ± 1.1
δ-receptor: 29 ± 10
κ-receptor: 0.9 ± 0.3

SUMMARY

NIH 11250 has very high affinity for the κ opioid receptor, and is 3- and 30-fold selective, respectively, for κ over μ and δ receptors.

NIH 11253 **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan. HCl**



HCl

OPIOID RECEPTOR BINDING (nM)

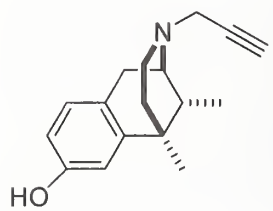
μ-receptor: 500 ± 170
δ-receptor: 1480 ± 390
κ-receptor: 157 ± 6

SUMMARY

NIH 11253 has low affinity for the κ and has only 3-fold selectivity over the μ opioid receptor and 9-fold selectivity over the δ opioid receptor.

* * *

NIH 11254 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan.HCl**



HCl

OPIOID RECEPTOR BINDING (nM)

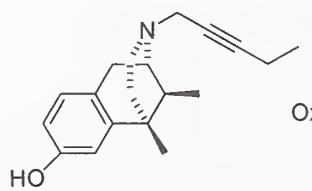
μ-receptor: 2.1 ± 0.8
δ-receptor: 4.5 ± 0.9
κ-receptor: 0.8 ± 0.2

SUMMARY

NIH 11254 has very high affinity for all three receptors, with little selectivity.

* * *

NIH 11255 **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate**



Oxalate

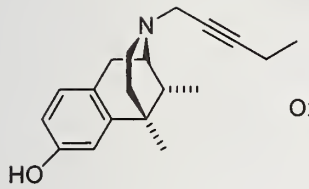
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 247 ± 31
δ-receptor: 3340 ± 310
κ-receptor: 71 ± 21

SUMMARY

NIH 11255 has affinity for the κ opioid receptor, with 47-fold selectivity for κ over δ but less than 4-fold selectivity for the κ vs. μ opioid receptor.

NIH 11256 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate**



Oxalate

OPIOID RECEPTOR BINDING (nM)

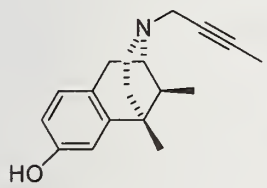
μ-receptor: 2.1 ± 0.4
δ-receptor: 134 ± 46
κ-receptor: 3.6 ± 0.9

SUMMARY

NIH 11256 has high affinity for the κ = μ opioid receptors, with 37- and 64-fold selectivity for these receptors over the δ opioid receptor.

* * *

NIH 11257 **(+)-(1*S*,5*S*,9*S*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate**



Oxalate

OPIOID RECEPTOR BINDING (nM)

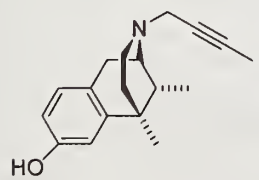
μ-receptor: 265 ± 37
δ-receptor: 3980 ± 20
κ-receptor: 97.3 ± 33.9

SUMMARY

NIH 11257 has low affinity for the κ and μ opioid receptors with little selectivity, but with a κ:δ selectivity of 40-fold.

* * *

NIH 11258 **(-)-(1*R*,5*R*,9*R*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate**



Oxalate

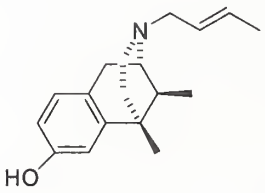
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1.9 ± 0.2
δ-receptor: 39 ± 12
κ-receptor: 2.0 ± 0.4

SUMMARY

NIH 11258 has high affinity for the κ and μ opioid receptors, with 20-fold selectivity for these over the δ opioid receptor.

NIH 11259 **(+)-(1*S*,5*S*,9*S*)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate**



Oxalate

OPIOID RECEPTOR BINDING (nM)

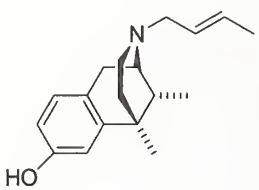
μ-receptor: 213 ± 63
δ-receptor: 6070 ± 1090
κ-receptor: 119 ± 10

SUMMARY

NIH 11259 has affinity for the κ ≥ μ opioid receptors, and is approximately 30-fold selective for these receptors over the δ opioid receptor.

* * *

NIH 11260 **(-)-(1*R*,5*R*,9*R*)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate**



Oxalate

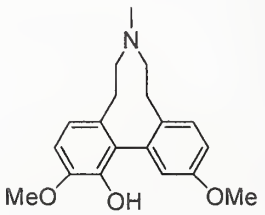
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3.2 ± 1.2
δ-receptor: 28.5 ± 6.8
κ-receptor: 2.2 ± 0.6

SUMMARY

NIH 11260 has high affinity for the μ = κ opioid receptors and is approximately 9-fold selective for these receptors over the δ opioid receptor.

NIH 11261 **(+)-Neodihydrothebaine.HCl**



HCl

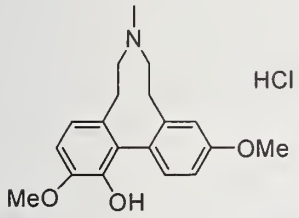
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 36 ± 5% inhibition at 10 μM
δ-receptor: 36 ± 2% inhibition at 10 μM
κ-receptor: 29 ± 8% inhibition at 10 μM

SUMMARY

NIH 11261 has no affinity for μ, δ, or κ opioid receptors.

NIH 11262 (+)-Bractazonine.HCl



OPIOID RECEPTOR BINDING (nM)

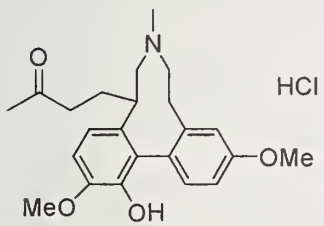
μ-receptor: 5250 ± 210
δ-receptor: 28 ± 14% inhibition at 10 μM
κ-receptor: 5270 ± 1560

SUMMARY

NIH 11262 has very low affinity for the μ and κ opioid receptors and no affinity for the δ opioid receptor.

* * *

NIH 11263 (+)-(3-Oxobutyl)bractazonine.HCl



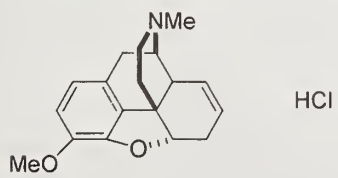
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1830 ± 460
δ-receptor: 1680 ± 220
κ-receptor: 13100 ± 1700

SUMMARY

NIH 11263 has very low affinity at the μ and δ opioid receptors with no affinity at the δ opioid receptor.

NIH 11264 6-Desoxycodeine.HCl



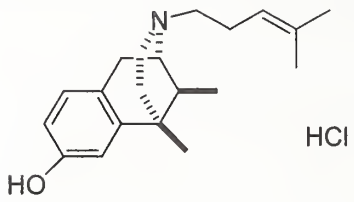
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 305 ± 79
δ-receptor: 3090 ± 150
κ-receptor: 4520 ± 710

SUMMARY

NIH 11264 has low affinity at the μ opioid receptor but with 10-fold selectivity over μ and 15-fold selectivity over κ opioid receptors.

NIH 11265 **(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

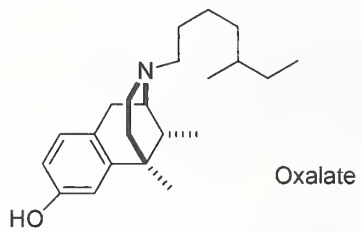
μ-receptor: 134 ± 17
δ-receptor: 1010 ± 240
κ-receptor: 271 ± 93

SUMMARY

NIH 11265 has low affinity at the μ and κ opioid receptors and with 3- to 7-fold selectivity over the δ opioid receptor.

* * *

NIH 11266 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan.oxalate**



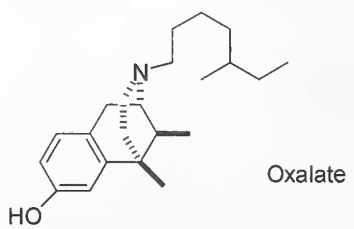
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 4.0 ± 1.8
δ-receptor: 42.0 ± 11.4
κ-receptor: 26.1± 6.7

SUMMARY

NIH 11266 has high affinity at the μ opioid receptor with 6-fold selectivity over κ and 10-fold selectivity over the δ opioid receptor.

NIH 11267 **(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan. oxalate**



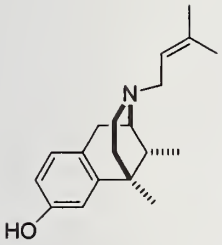
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 307 ± 67
δ-receptor: 2910 ± 230
κ-receptor: 94.1 ± 12.8

SUMMARY

NIH 11267 has affinity at the κ opioid receptor, with 3-fold selectivity over μ and 30-fold selectivity over the δ opioid receptor.

NIH 11268 **(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan. oxalate**



Oxalate

OPIOID RECEPTOR BINDING (nM)

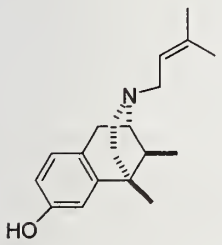
μ-receptor: 5.6 ± 0.8
δ-receptor: 110 ± 18
κ-receptor: 12.5 ± 4.5

SUMMARY

NIH 11268 has high affinity at the μ opioid receptor and similar affinity at the κ opioid receptor. It is 9- to 20-fold selective for these over the δ opioid receptor.

* * *

NIH 11269 **(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan. oxalate**



Oxalate

OPIOID RECEPTOR BINDING (nM)

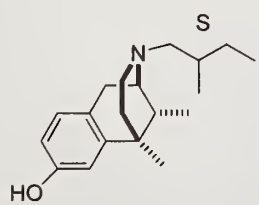
μ-receptor: 307 ± 25
δ-receptor: 4550 ± 750
κ-receptor: 65.3 ± 9.2

SUMMARY

NIH 11269 has affinity at the κ opioid receptor with 4-fold selectivity over μ opioid receptors and 70-fold selectivity over δ opioid receptors.

* * *

NIH 11270 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan.HCl**



HCl

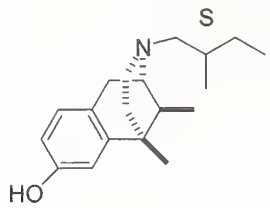
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 5.3 ± 0.3
δ-receptor: 21.9 ± 4.4
κ-receptor: 2.8 ± 0.1

SUMMARY

NIH 11270 has high affinity at the μ ≥ κ opioid receptors and is 4- to 8-fold selective for these over the δ opioid receptor.

NIH 11271 **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-[(*S*)-2-methylbutyl]-6,7-benzomorphan. HCl**



OPIOID RECEPTOR BINDING (nM)

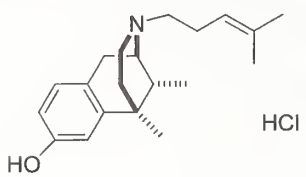
μ-receptor: 555 ± 50
δ-receptor: 5870 ± 860
κ-receptor: 47.5 ± 17.5

SUMMARY

NIH 11271 has affinity at the κ opioid receptor with 11-fold selectivity over the μ opioid receptor and 120-fold selectivity over the δ opioid receptor.

* * *

NIH 11272 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan. HCl**



OPIOID RECEPTOR BINDING (nM)

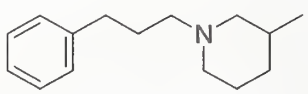
μ-receptor: 0.97 ± 0.14
δ-receptor: 6.0 ± 1.7
κ-receptor: 6.6 ± 0.9

SUMMARY

NIH 11272 has very high affinity at μ opioid receptor with 6-fold selectivity over δ and κ opioid receptors.

* * *

NIH 11273 **3-Methyl-1-(3-phenylpropyl)piperidine.oxalate**



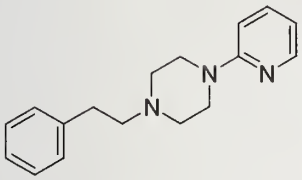
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 22% inhibition at 10 μM
δ-receptor: 27% inhibition at 10 μM
κ-receptor: 9% inhibition at 10 μM

SUMMARY

NIH 11273 has no affinity at μ, δ, or κ opioid receptors.

NIH 11274 1-(2-Phenethyl)-4-(2-pyridyl)piperazine.oxalate



OPIOID RECEPTOR BINDING (nM)

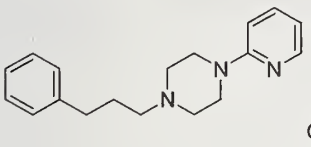
μ-receptor: 1140 ± 20
δ-receptor: 29% inhibition at 10 μM
κ-receptor: 17% inhibition at 10 μM

SUMMARY

NIH 11274 has very low affinity at the μ opioid receptor and no affinity at δ or κ opioid receptors.

* * *

NIH 11275 1-(3-Phenylpropyl)-4-(2-pyridyl)piperazine.oxalate



OPIOID RECEPTOR BINDING (nM)

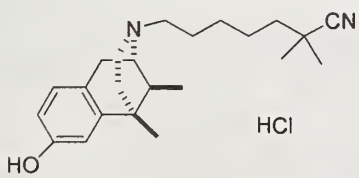
μ-receptor: 454 ± 64
δ-receptor: 29% inhibition at 10 μM
κ-receptor: 6030 ± 590

SUMMARY

NIH 11275 has low affinity at the μ opioid receptor with 13-fold selectivity over κ opioid receptors and no affinity at δ opioid receptors.

* * *

NIH 11285 (+)-(1*S*,5*S*,9*S*)-2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



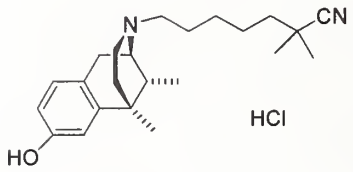
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 383 ± 106
δ-receptor: 3070 ± 620
κ-receptor: 533 ± 5

SUMMARY

NIH 11285 has low affinity at μ and κ opioid receptors with 6- to 8-fold selectivity for these over δ opioid receptors.

NIH 11286 **(-)-(1*R*,5*R*,9*R*)-2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

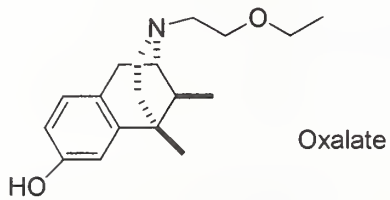
μ-receptor: 9.4 ± 1.1
δ-receptor: 39.2 ± 8.6
κ-receptor: 76.5 ± 5.0

SUMMARY

NIH 11286 has high affinity at the μ opioid receptor, but with only 4- to 8-fold selectivity over δ and κ opioid receptors.

* * *

NIH 11287 **(+)-(1*S*,5*S*,9*S*)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomophan.oxalate**



OPIOID RECEPTOR BINDING (nM)

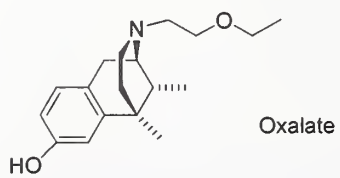
μ-receptor: 201 ± 44
δ-receptor: 2640 ± 310
κ-receptor: 219 ± 34

SUMMARY

NIH 11287 has low affinity at μ and κ opioid receptors with 12-fold selectivity for these over the δ opioid receptor.

* * *

NIH 11288 **(-)-(1*R*,5*R*,9*R*)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate**



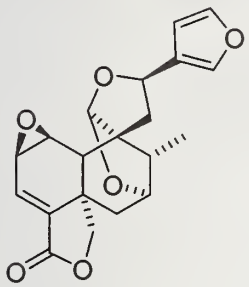
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1.2 ± 0.3
δ-receptor: 29.6 ± 1.7
κ-receptor: 2.0 ± 0.2

SUMMARY

NIH 11288 has high affinity at μ and κ opioid receptors and affinity with approximately 15-fold selectivity over the δ opioid receptor.

NIH 11297 **Compound from Sage**



OPIOID RECEPTOR BINDING (nM)

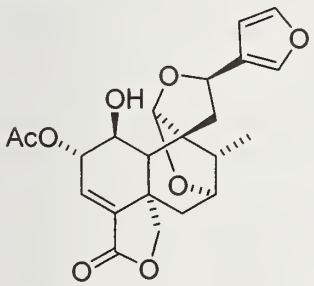
μ-receptor: 22% inhibition at 10 μM
δ-receptor: 0% inhibition at 10 μM
κ-receptor: 3% inhibition at 10 μM

SUMMARY

NIH 11297 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11298 **Compound from Sage**



OPIOID RECEPTOR BINDING (nM)

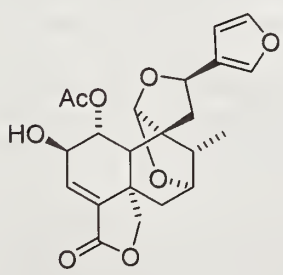
μ-receptor: 16% inhibition at 10 μM
δ-receptor: 11% inhibition at 10 μM
κ-receptor: 12% inhibition at 10 μM

SUMMARY

NIH 11298 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11299 **Compound from Sage**



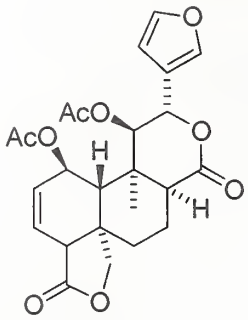
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 22% inhibition at 10 μM
δ-receptor: 12% inhibition at 10 μM
κ-receptor: 10% inhibition at 10 μM

SUMMARY

NIH 11298 has no affinity at μ, δ, or κ opioid receptors.

NIH 11300 **Compound from Sage**



OPIOID RECEPTOR BINDING (nM)

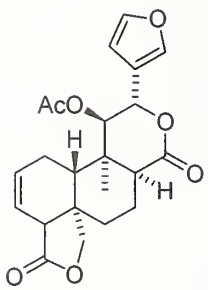
μ-receptor: 28% inhibition at 10 μM
δ-receptor: 16% inhibition at 10 μM
κ-receptor: 20% inhibition at 10 μM

SUMMARY

NIH 11300 has no affinity at μ, δ, or κ opioid receptors

* * *

NIH 11301 **Compound from Sage**



OPIOID RECEPTOR BINDING (nM)

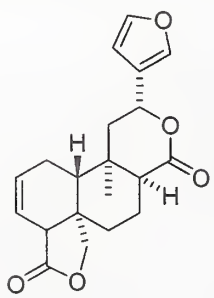
μ-receptor: 14% inhibition at 10 μM
δ-receptor: 10% inhibition at 10 μM
κ-receptor: 1% inhibition at 10 μM

SUMMARY

NIH 11301 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11302 **Compound from Sage**



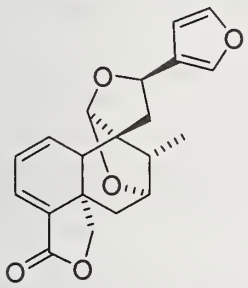
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 16% inhibition at 10 μM
δ-receptor: 7% inhibition at 10 μM
κ-receptor: 5% inhibition at 10 μM

SUMMARY

NIH 11302 has no affinity at μ, δ, or κ opioid receptors.

NIH 11303 Sage



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 18% inhibition at 10 μM
δ-receptor: 0% inhibition at 10 μM
κ-receptor: 0% inhibition at 10 μM

SUMMARY

NIH 11303 has no affinity at μ, δ, or κ opioid receptors.

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ACKNOWLEDGMENTS

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AFFILIATION

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APPENDIX

The University of Michigan laboratories also offer the following tests under the auspices of the Drug Evaluation Committee:

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts l5-min and consists of an initial l0-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than l00 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete, 15-min cycles. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively (*i.e.*, fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone)

during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that one training cycle, and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization usually occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.*, irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.*, alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (*i.e.*, precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (*i.e.*, withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40°C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The inter-injection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.*, alfentanil) or κ (*e.g.*, U-50,488) opioid agonist.

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject alfentanil. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding is obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produces an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989 and 1992). Procedures in which a single dose point is available as a comparison compound can be customized to accommodate drugs that may have pharmacokinetics different from alfentanil.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 l/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g.*, alfentanil).

EVALUATION OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2006)

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The identity of compounds submitted by the Biological Coordinator, Dr. Andrew Coop, of the University of Maryland was unknown to us. These studies were conducted under the auspices of the Drug Evaluation Committee in association with the College on Problems of Drug Dependence. See summary of new data in Table 1. All animals received care according to the "Guide for the Care and Use of Laboratory Animals" (1996). These facilities are certified by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). Supported by NIDA Contract DA 1-7725.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used. Beginning with NIH 11256, the dose regimen of morphine sulfate was changed from 3 mg/kg s.c. daily every six hours at 6 AM, 12 noon, 6 PM and midnight to 4 mg/kg, s.c. daily at 6 AM, 12 noon and 6 PM. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. Unless otherwise noted, at least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 hr and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 4.0 mg/kg; and c) vehicle control, 1 ml/kg. Withdrawal signs were scored, absent or present, once during each of five consecutive 30 min observation periods. Withdrawal signs included: slowing of movement, drowsiness (sitting with eyed closed and lethargic or being indifferent to surroundings), fighting, vocalizing, rigidity of abdominal muscles, vocalization during palpation of abdominal muscles, restlessness (pacing), tremors, coughing, retching, vomiting, wet-dog shakes and masturbation. The observer was "blind" regarding the assignment of treatments. The mean cumulative score ± SEM was calculated for each observation period and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis ANOVA and post hoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 hr after the last dose of morphine. These animals were not then in withdrawal. Naloxone·HCl (0.06 mg/kg, s.c.) served as the positive control.

Table 1. List of NIH compounds included in this report as well as an indication of the tests that were conducted on each compound

NIH #	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
8508	2-Methylmorphan	T	T	T	T	T	
8509	2-Methylmorphan	T	T	T	T	T	
11056	Morphinan	T	T	T	T	T	
11184	Methylmorphinan	T	T	T	T	T	
11193	Peptide	T	T	T	T		
11231	6,7 Benzomorphan	T	T	T	T	T	
11232	6,7-Benzomorphan	T	T	T	T		
11233	6,7-benzomorphan	T	T	T	T		
11234	6,7-Benzomorphan	T	T	T	T		

Table 1. (continued)

NIH #	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
11236	6,7-Benzomorphan	T	T	T	T	T	
11237	6,7-Benzomorphan	T	T	T	T	T	
11249	6,7-Benzomorphan	T	T	T	T	T	
11250	6,7-Benzomorphan	T	T	T	T	T	
11553	6,7-Benzomorphan	T	T	T	T		
11250	6,7-Benzomorphan	T	T	T	T		T
11250	6,7-Benzomorphan	T	T	T	T		T
11250	6,7-Benzomorphan	T	T	T	T		T
11257	6,7-Benzomorphan	T	T	T	T		T
11250	6,7-Benzomorphan	T	T	T	T	T	
11259	6,7-Benzomorphan	T	T	T	T		T
11260	6,7-Benzomorphan	T	T	T	T		
11261	Neohydrothebaine	T	T	T	T		
11262	Bractazonine	T	T	T	T		
11263	Oxobutylbractazonine	T	T	T	T		
11265	6,7-Benzomorphan	T	T	T	T		
11260	6,7-Benzomorphan	T	T	T	T	T	
11269	6,7-Benzomorphan	T	T	T	T		
11270	6,7-Benzomorphan	T	T	T	T	T	
11272	6,7-Benzomorphan	T	T	T	T	T	
11276	CP55490			T			
11277	Win 55,212-2			T			

T = Tested

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with the antagonist, naloxone, or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with nylon sutures and attached to a flow-through swivel mechanism that allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe that was attached to a syringe pump. The animals received 4-8 ml of solution every 24 hr. During withdrawal, the following signs were noted: irritability; front-paw shakes; wet-dog shakes; facial rubbings with front paws; eyelid ptosis and immobility.

Substitution-for-Morphine (SM) Test. The rats received morphine·SO_4 (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 hr at 6, 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received the test compound, at appropriate doses, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male ICR mice, weighing 20-30 g, were used. All drugs were dissolved in sterile water or in a suitable vehicle and usually injected by the subcutaneous (s.c.) route of administration. Other routes of administration, when employed, are indicated in the report. At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's or AD50's were calculated by using computerized probit analysis (Bliss, 1967). The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.), intravenously (i.v.), or intracerebroventricular (i.c.v) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove, which contained a slit under which was located a photoelectric cell. When the heat source or noxious light stimulus was turned on, it focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed though the slit and activated the photocell which in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 sec under control conditions. Mice were injected with drug or vehicle and tested 20 min later. In the assays for antagonism of the antinociceptive effect, the potential antagonists were administered 10 min before the agonist, and evaluation occurred 20 min later.

Table 2. Comparative Data (ED50, mg/kg, s.c. and 95% C.L. of Selected Standards in 4 Mouse Agonist-Antagonist Assays

Drug	Assays ED50 (95% C.L.) or % change, mg/kg/ s.c			
	TF	TF Antagonist	Phenylquinone	Hot -Plate
Pentazocine	15% at 10	18 (12 - 26)	1.7 (1.0 – 2.5)	13% at 30
Cyclazocine	17% at 1	0.03 (0.02 – 0.78)	0.01 (0.005 – 0.03)	25% at 9
Naloxone HCl	None at 10	0.04 (0.02 – 0.09)	Inactive	---
Naltrexone HCl	None at 10	0.007 (0.002 – 0.02)	Inactive	---
Morphine SO_4	1.92 (0.89 – 4.14)	Inactive	0.4 (0.2 – 0.8)	0.85 (0.39 – 1.86)
Codeine PO_4	17.5 (15.4 – 19.9)	Inactive	8.25 (5.12 – 13.29)	6.4 (0.39 – 16.8)
Enadoline HCl Kappa agonist NIH 10672	0.015 (0.003 – 0.059)	Inactive	0.0015 (0.004 – 0.006)	0.01 (0.004 – 0.04)
(+)-SNC80 NIH 10815 Delta agonist	Inactive	Inactive	3.8 (1.6 – 9.3)	Inactive

Table 2. (continued)

Drug	Assays ED50 (95% C.L.) or % change, mg/kg/ s.c			
	TF	TF Antagonist	Phenylquinone	Hot -Plate
Sufentanil citrate NIH 9726 Mu agonist	0.004 (0.002 – 0.009)	---	---	---

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drug and 10 min later received 2.0 mg/kg intraperitoneally (i.p.) of a freshly prepared paraphenylquinone (PPQ) solution (0.2 mg/ml), The mice were then placed in cages in groups of three each. Ten min after the PPQ injection, the total number of stretches per group were counted over 1-min periods. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the hindlimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 56°C. Mice were placed on the hot plate and activity was scored if the animal jumped, lifted its back feet, or licked its front paws.

Calculation of Apparent pA2. Using the tail-flick or PPQ assay, the apparent pA_2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY, 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. The mice were tested 30 min after receiving the antagonist. Dose response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED5Os were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x - 1) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x - l) were plotted. The pA_2 values for the antagonists were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

Treatment	Schild Plot	Constrained Plot
Antagonist/Agonist	pA_2 (95% C.L.) Slope	pA_2(95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1 - 7.6)
2) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
3) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
4) Naloxone/NIH 10672 (Enadoline) (selective kappa agonist)	6.1 (5.6 - 6.6)-1.2	6.6 (6.3 - 7.0)
5) Naloxone/U-50,488 (kappa agonist)	6.6 (6.3 - 6.9)-1.1	6.2 (5.9 - 7.3)
6) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	-
7) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
8) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
9) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 - 7.6)
10) (-)-Quadazocine/Enadoline	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
11) nor BNI/Enadoline	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
12) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	-

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multi-receptors, receptor sensitization, pre-coupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to a slope of - 1.

Table 4. AD50s of selective opioid antagonists versus opioid agonist ED80s

Selective Antagonist	Antagonist Pretreatment time	Agonist	Agonist ED80 Pretreatment time	Assay	Antagonist AD50 95% C.L.
beta-FNA i.c.v. mu	4 hr	Sufentanil NIH 9726 s.c.	20 min	TF	3.98 (1.24 – 12.89) µg/brain
		Morphine s.c.			1.25 (0.56 – 2.78) µg/brain
Naltrindole NIH 10589 s.c. delta	30 min	SNC 80 NIH 10815 s.c.	20 min	PPQ	5.48 (2.97 – 10.11) mg/kg

Table 4. (continued)

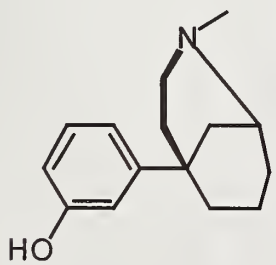
Naltrindole i.c.v. delta		DPDPE NIH 10892 i.c.v.	10 min	PPQ	1.38 0.41 – 4.68 μg/brain
nor-BNI NIH 10588 s.c. kappa	2 hr	Enadoline NIH10672 s.c.	20 min	TF	10.26 (4.14 – 25.38) mg/kg
		(-)-U-50488 NIH 10533 s.c.			1.72 (0.57 – 5.16) mg/kg

Special Intracerebroventricular (i.c.v.) Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ test and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to test drugs that did not cross the blood-brain barrier.

Special in vivo opioid agonist and antagonist subtype testing. To further characterize opioids, special subtype testing is conducted. Results obtained with selective opioid antagonists vs standard mu-,kappa- and delta agonists are presented in Table 4.

Supported by NIDA Contract DA 1-7725. Conducted under the auspices of the Drug Evaluation Committee (DEC) in association with The College on Problems of Drug Dependence (CPDD)

NIH 8508 (-)-5-(*m*-Hydroxyphenyl)-2-methylmorphan.HCl



HCl

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** - a) 3.75 (2.12 – 6.63)
b) 5.4 (2.1 – 13.9)
c) 6.1 (1.9 – 19.3)

2) **TF vs. M** – a) Inactive at 1 and 10
b) Inactive at 1 and 10
c) 27% at 1 and 21% at 30

3) **PPQ** – a) 0.9 (0.03 – 2.4)
b) 0.9 (0.4 – 2.0)
c) 1.3 (0.3 – 6.0)

4) **HP** - a) 1.7 (1.2 – 2.4)
b) 2.0 (1.4 – 2.8)

NIH 8508 (continued)

Opioid Subtype Testing:

AD50 or % antagonism by opioid subtype antagonists vs ED80 of NIH 8508 (s.c.) in TF		
beta-FNA (mu) i.c.v.; μg/brain	**norBNI (kappa) mg/kg/s.c.**	**Naltrindole (delta) mg/kg/ s.c.**
0.33 (0.16 – 0.4)	**14% at 1; 19% at 10; and 8% at 30. Inactive**	**18% at 1; 34% at 3; 43% at 10 and 52% at at 30**

MONKEY DATA – SDS

Apparently, NIH 8508 produced a biphasic dose-response. It was inactive at the low dose (1.25 mg/kg), attenuated withdrawal at 5 mg/kg, and was inactive at 10 mg/kg. However, it did not substitute completely for morphine.

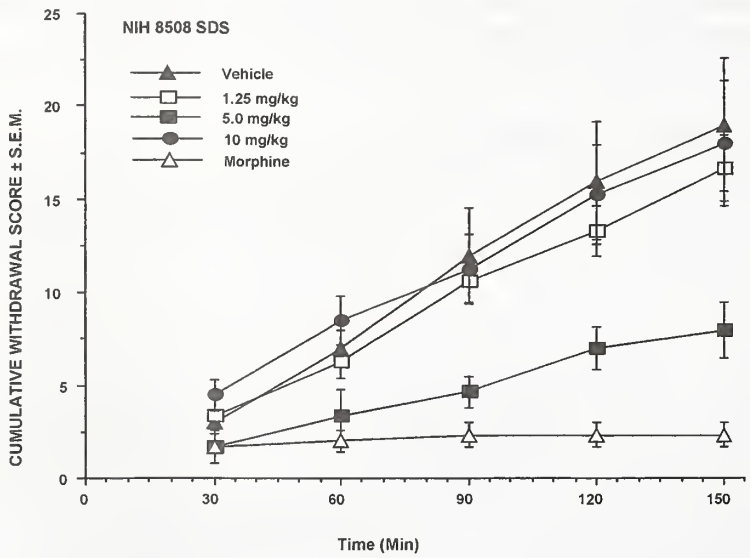
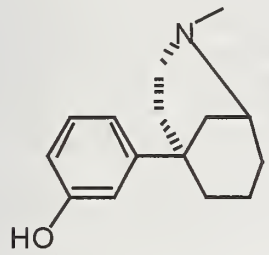


Fig. **NIH 8508-SDS-** Results of study in which single doses of NIH 8508 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment:.The mouse data suggest that NIH 8508 is a mu-opioid agonist with some delta-opioid agonist effects. It lacks kappa-opioid agonist activity as well as opioid antagonist effects. The monkey data is at odds with the mouse data. Normally, drugs with potent mu-opioid agonist activity will substitute completely for morphine in morphine-dependent monkeys in withdrawal.

NIH 8509 (+)-5-(m-Hydroxyphenyl)-2-methylmorphan.HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** - 4.8 (1.5 – 15.5)
2) **TF vs. M** - 0% at 1 and 18% at 30
3) **PPQ** - 0.5 (0.3 – 0.9)
4) **HP** - 0.35 (0.28 - 0.45)

Opioid Subtype Testing:

AD50 or % antagonism by opioid subtype antagonists vs ED80 of NIH 8509 (s.c.) in TF		
beta-FNA (mu) i.c.v.; µg/brain	**norBNI (kappa) mg/kg/s.c.**	**Naltrindole (delta) mg/kg/ s.c.**
0.28 (0.13 – 0.61)	**22% at 1; 24% at 10; and 30% at 30**	**0% at 1; 35% at 10 and 31% at 30**

MONKEY DATA – SDS

A dose-related suppression of withdrawal signs was observed in monkeys receiving 2 and 8 mg/kg of NIH 8509 (see accompanying Fig below). At the high dose, slowing and ataxia were observed in one of three monkeys tested. Previous work (NIDA Mono. Series 41,1982, p. 374) indicated similar results but less potency in the monkey SDS studies.

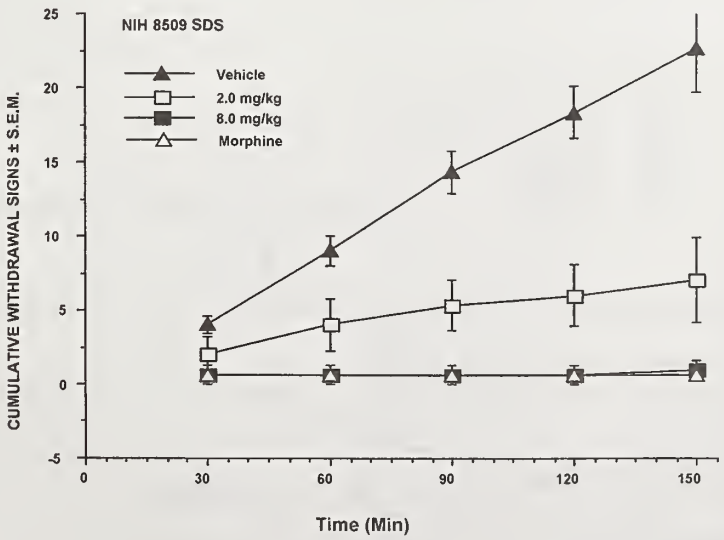
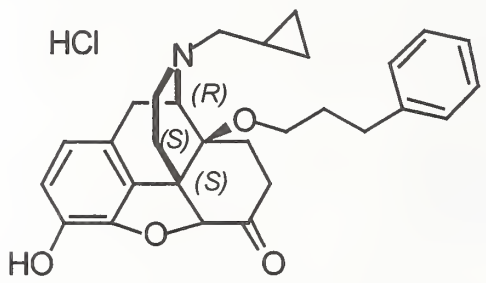


Fig. NIH 8509-SDS- Results of study in which single doses of NIH 8509 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: It appears that NIH 8509 has strong mu-opioid and rather weak kappa- and delta-opioid agonist effects.

NIH 11056A 17-Cyclopropylmethyl-4,5 -epoxy-14 -(3-phenylpropyloxy)morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50
(95% C. L.) mg/kg or % change

1) **TF** - 0.0032 (0.0016 - 0.0062)
2) **TF vs. M** – 14% at 1, 18% at 10 and 47% at 30
3) **PPQ** – 0.0062 (0.0031 -0.0125)
4) **HP** - 0.0023 (0.0011 - 0.0047)

Vehicle was 1% lactic acid aqueous solution. Straub tail and increased locomotor activity observed. Mild sedation at 10 and marked sedation at 30.

Duration of Action Study Using 80% Response Dose of NIH 11056 in Tail Flick Test

Pretreatment Time	%MPE
20 min	70
2 hr	93
4 hr	70
6 hr	70
15 hr	38
24 hr	0

MONKEY DATA (SDS)

As depicted in the figure below, NIH 11056A substituted completely for morphine at 0.04 mg/kg s.c. Potency estimate is approximately 100 times that of morphine sulfate. Jaw sag and scratching were noted in 1 monkey receiving 0.02 mg/kg s.c.

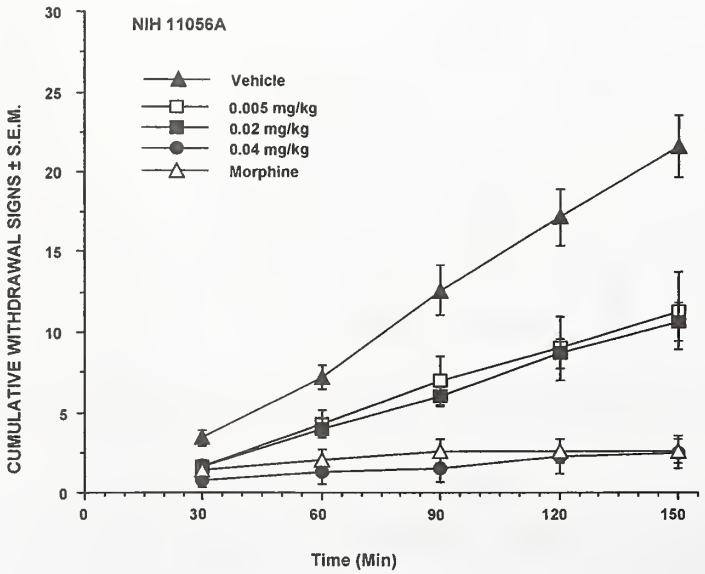
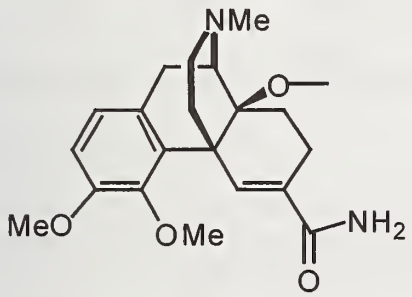


Fig. NIH 11056A SDS- Results of study in which single doses of NIH 11056A were substituted for morphine in morphine-dependent monkeys in withdrawal

NIH 11056A (continued)

Comment: The mouse and monkey data indicate that NIH 11056 is a potent opioid agonist with prominent mu-opioid receptor properties. Potency estimate in the mouse is approximately 3000 times that of morphine sulfate. However, in the monkey potency estimate is about 100 times that of the reference standard. Duration of analgesic activity in the mouse was at least 15 hr.

NIH 11184 5,6-Didehydro-3,4,14-trimethoxy-17-methylmorphinan-6-carboxamide



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) **TF** – 11% at 1 and 37% at 10
2) **TF vs. M** – 13% at 1 and 0% at 10
3) **PPQ** – 0.18 (0.08 – 0.43)
4) **HP** – 13% at 1, 13% at 3, 50% at 10 and 30

Comment: At the doses tested, NIH 11184 does not possess remarkable mu-opioid activity. Drug supply was exhausted.

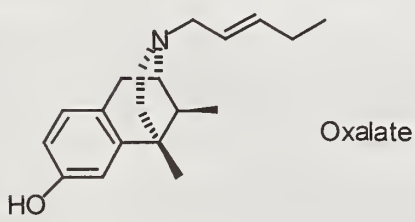
NIH 11193 (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methyl(4αR)-1,3,4,9,10,10a-α-hexhydro[2H]-10a,4α-(imnoethano)phenanthrene-3-ol, 6-(1,4-dioxo)-butanediyl-3-[α-N-acetyl, ε-imino-(lysyl)]-des-1-arginyl, des-2-prolyl-substance P

MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 38% at 1, inactive at 10 and 30
3) **PPQ** – Inactive at 1, 28% at 10 and 49% at 30
4) **HP** – Inactive at 1, 10 and 30

Comment: The results in mice do not predict opioid effects.

NIH 11231 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan·oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 7% at 1, 15% at 10 and 55% at 30
3) **PPQ** – 1.63 (0.49 – 5.49)
4) **HP** – 26% at 1, 36% at 10 and inactive at 30

MONKEY DATA – SDS

As shown in the accompanying figure, at doses of 2.5 and 10 mg/kg, NIH 11231 did not attenuate withdrawal, substitute for morphine or exacerbate withdrawal.

NIH 11231 (continued)

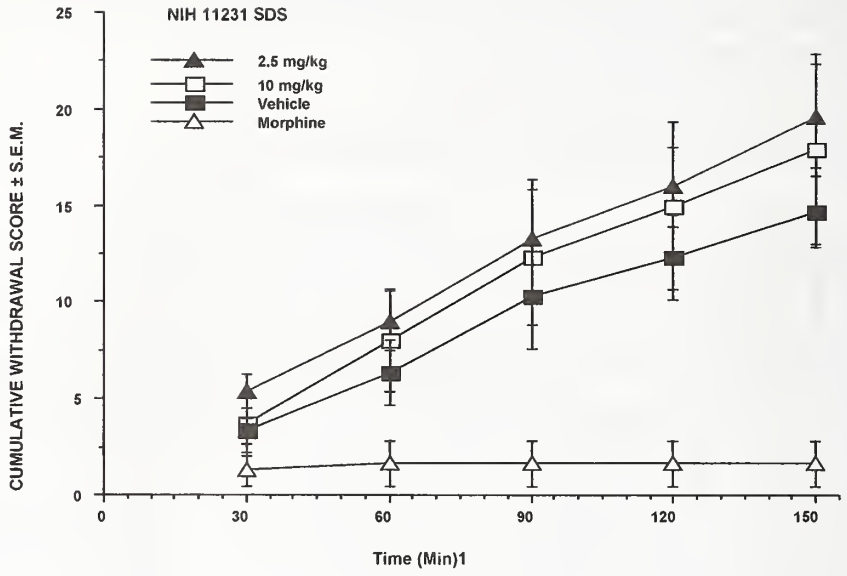
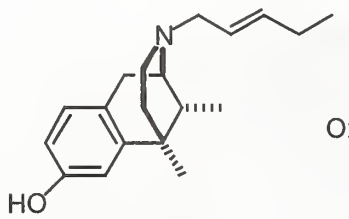


Fig NIH 11231 SDS - Results of study in which single doses of NIH11231 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: These results do not predict significant mu- or kappa-opioid agonist activity.

NIH 11232 (-)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7- benzomorphan·oxalate



Oxalate

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1 and 10 and 16% at 30
2) **TF vs. M** – 1.87 (0.65 – 5.34)
3) **PPQ** – 0.74 (0.34 – 1.61)
4) **HP** – 6% at 0.3, 48% at 1, 33% at 3, inactive at 10 and 55% at 30

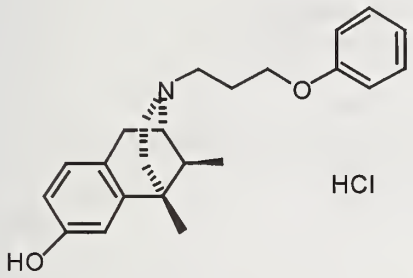
Vehicle was 15% Hydroxypropyl-beta-cyclodextrin in water.

Opioid Subtype Testing:

AD50 or %Antagonism by an opioid antagonist vs ED50 of NIH 11232 in the PPQ test	
Naltrindole (delta) s.c.	Inactive at 1, 19% at 10 and inactive at 30

Comment: NIH 11232 has weak opioid –antagonist properties and is essentially inactive as a delta-opioid agonist.

NIH 11233 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1 and 10, 24% at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 2.76 (2.17 – 3.50
4) **HP** – Inactive at 1, 10 and 30

Sedation noted at higher doses. Vehicle was 15% Hydroxypropyl-beta–cyclodextrin in water.

MONKEY DATA – SDS

NIH 11233 substituted completely for morphine at the high dose (see figure). The drug acted quickly and its duration of action was at least as long as that of morphine sulfate. Some slowing was noted at both doses and eyelid ptosis was observed at the high dose. Vehicle was 10% Hydroxypropyl-beta-cyclodextrin.

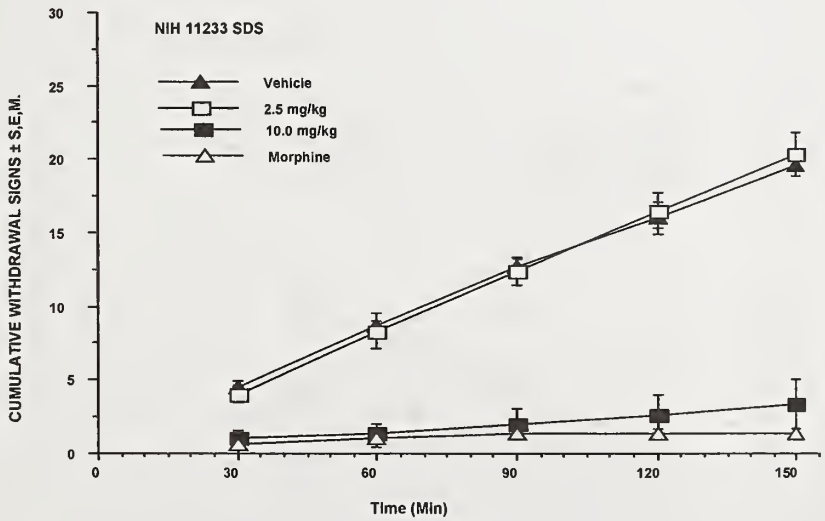
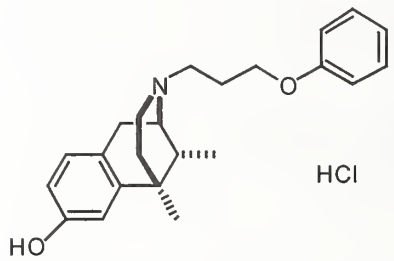


Fig NIH 11233-SDS - Results of study in which single doses of NIH 11233 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: To say the least, the results are unusual. There is little evidence, in mice, that NIH 11233 has opioid activity. In sharp contrast, the drug substituted completely for morphine in the morphine-dependent monkeys in withdrawal. This apparent inconsistency should be investigated further.

NIH 11234 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 2.09 (1.47 – 2.98)
2) **TF vs. M** – Inactive at 1 and 10, 18% at 30
3) **PPQ** – 0.42 (0.57 – 1.36)
4) **HP** – 0.64 (0.49 – 0.83)

Straub tail and increased locomotor activity were noted. Vehicle was 15% Hydroxy-propylbeta-cyclodextrin in water.

MONKEY DATA – SDS

One monkey that received 10 mg/kg convulsed. Pentobarbital quickly terminated the convulsion Otherwise, at 2.5 mg/kg, in two of three monkeys, NIH 11234 substituted for morphine. The standard error for the high dose was large (see figure) because one monkey had a high withdrawal sign score. Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in sterile water.

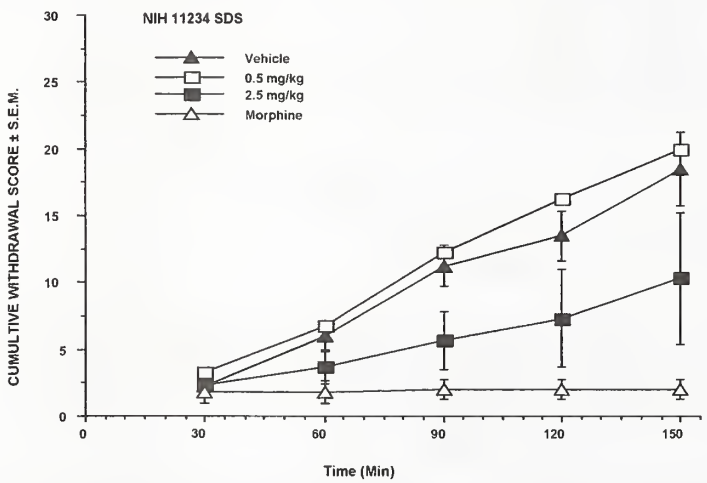
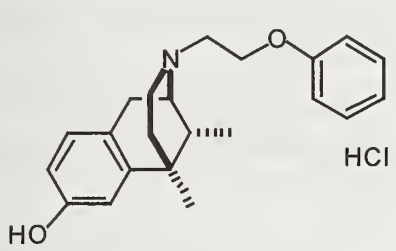


Fig NIH 11234-SDS - Results of study in which single doses of NIH 11234 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11134 displays mu-opioid agonist properties. Whether or not the convulsion was opioid related remains to be determined.

NIH 11236 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-phenoxyethyl)-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 9.60 (5.7 – 16.2)
2) **TF vs. M** – 10% at 1, inactive at 10 and 7% at 30
3) **PPQ** – 4.80 (4.30 – 5.35)
4) **HP** – 16% at 1 and 3, 28% at 10 and 64% at 30

MONKEY DATA – SDS

As shown below in the figure, at the high dose, NIH 11236 reduced the number of withdrawal signs in morphine-dependent monkeys in withdrawal. At this dose, the withdrawal signs slowing and ataxia were also noted. Apparently, the duration of action is shorter than that of morphine sulfate, the reference standard. Potency estimate is about 1/3 that of morphine sulfate.

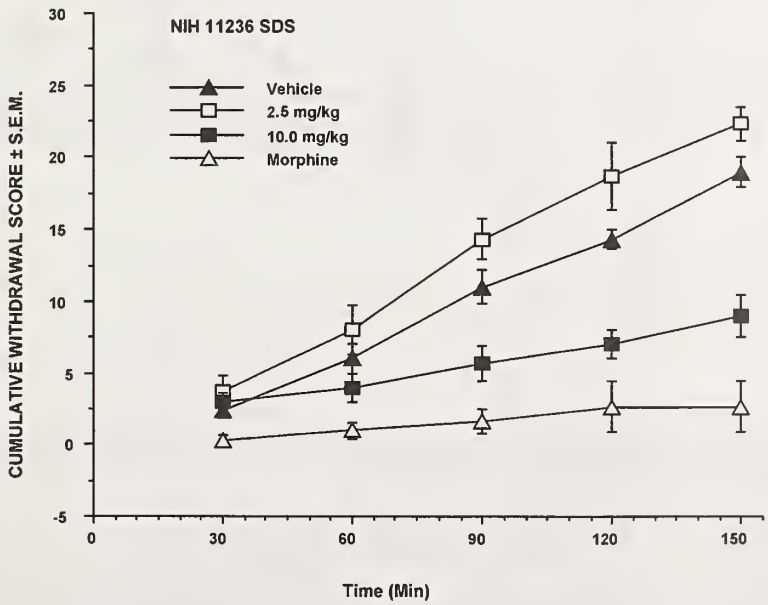
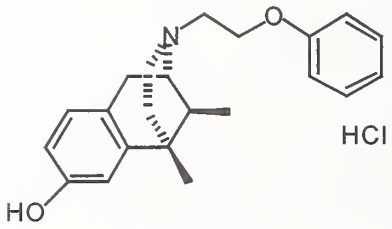


Fig NIH 11236-SDS - Results of a study in which single doses of NIH 11236 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: All in all, the results indicate that NIH 11236 has mu-opioid activity.

NIH 11237 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-phenoxyethyl)-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10% at 10 and inactive at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 6.8 (range not determined)
4) **HP** – 13.6 (7.1 – 26.2)

MONKEY DATA – SDS

As shown in the figure, at doses of 2.5 and 10 mg/kg, NIH did not substitute for morphine or attenuate or exacerbate withdrawal.

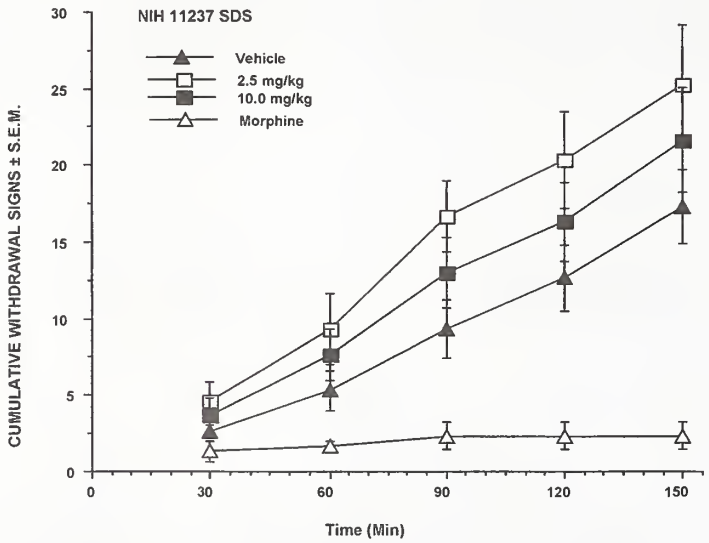
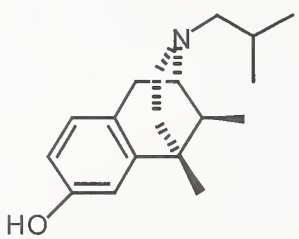


Fig NIH 11237-SDS - Results of study in which single doses of NIH111237 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The data suggest very weak, if any, opioid agonist or antagonist activity.

NIH 11249 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan·HBr



HBr

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10 and 20
2) **TF vs. M** – 44% at 1, inactive at 10 and 30
3) **PPQ** – 33% at 1, 32% at 10 and 30% at 30
4) **HP** – Inactive at 1, 6% at 10 and inactive at 30

Elevated tail and increased locomotor activity were noted. Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in water.

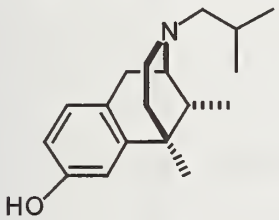
NIH 11249 (continued)

MONKEY DATA – SDS

A limited drug supply precluded a full study. Preliminary work indicated little, if any effects in the SDS test.

Comment: The results in mice suggest some weak CNS stimulatory activity.

NIH 11250 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr



HBr

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 27% at 1, 13% at 10 and 29% at 30
2) **TF vs. M** – 20% at 0.3, 69% at 1, 70% at 10 and 47% at 30
3) **PQ** – 0.83 (0.52 – 1.31)
4) **HP** – 32% at 1, 43% at 3, 49% at 10 and 65% at 30

Straub tail, ataxia, loss of righting reflex, immobility and convulsions were observed.

Vehicle was 15% Hydroxypropyl-beta-cyclodextrin in water.

MONKEY DATA – SDS

At doses of 0.05 and 0.2 mg/kg, NIH 11250 produced a dose-related attenuation of withdrawal signs (see Figure below). However at the high dose, slowing and ataxia were also noted.

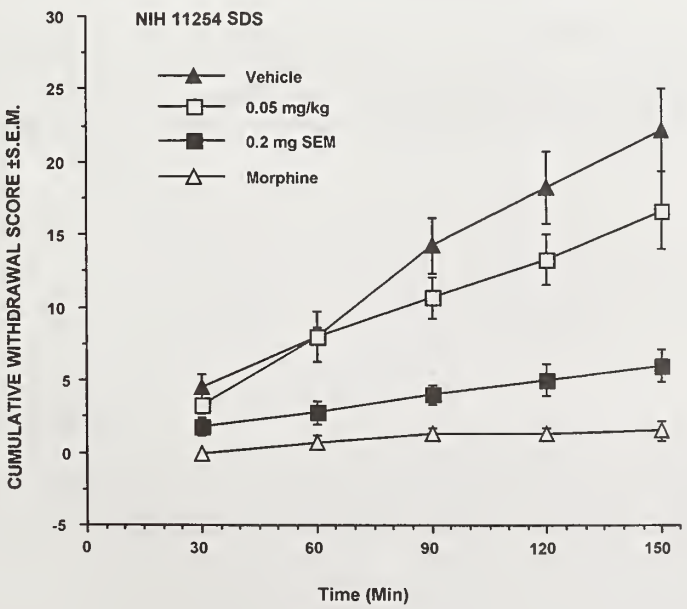
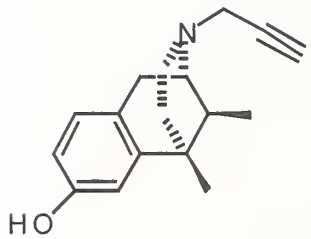


Fig NIH 11250-SDS. Results of study in which single doses of NIH 11250 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Although the drug attenuated withdrawal, CNS activity obscured the evaluation of NIH 11250.

NIH 11253 (+)-(1*S,5S,9S*)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan·HCl



HCl

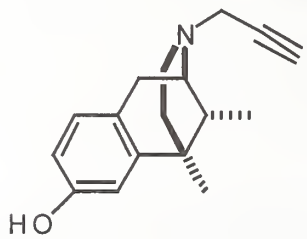
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 24% at 10 and 13% at 30
2) **TF vs. M** – 8.9 (3.8 – 21.0)
3) **PPQ** – 6.72 (4.64 – 11.1)
4) **HP** – 30% at 1, 13% at 10 and inactive at 30

Straub tail and ataxia were noted.

Comment: NIH 11253 has weak opioid-antagonist properties.

NIH 11254 (-)-(1*R,5R,9R*)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan·HCl



HCl

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 14% at 1, 3% at 10 and12% at 30
2) **TF vs. M** – 0.16 (0.05 – 0.58)
3) **PPQ** – 2.07 (0.34 – 10.8)
4) **HP** – 20% at 1, 57% at 10, 7% at 30

Straub tail, loss of righting reflex, increased locomotor activity and ataxia were noted.

MONKEY DATA – PPt-W

NIH 11254 was tested for opioid antagonist activity at doses of 1 and 4 mg/kg.

The drug promptly precipitated withdrawal and duration of action was at least 2.5 hr. However, as shown in the figure below, the effects at both doses appear to be maximal and estimates of potency would not be reliable.

NIH 11254 (continued)

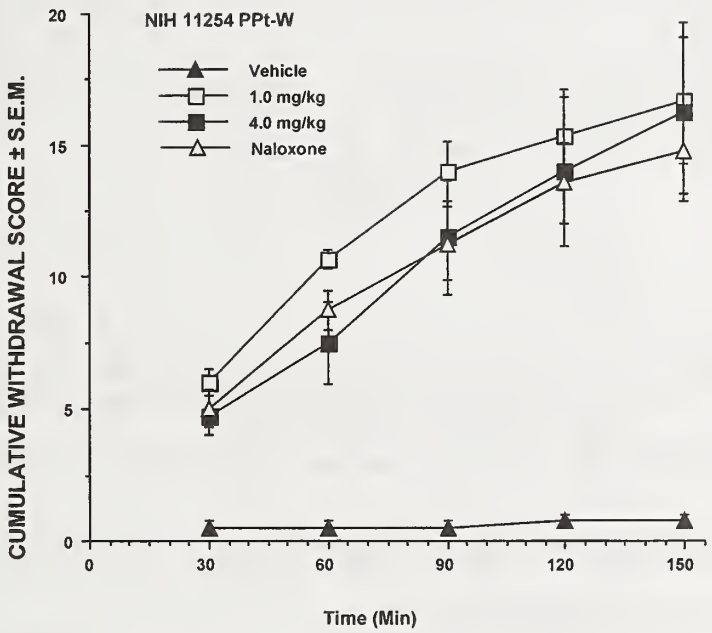
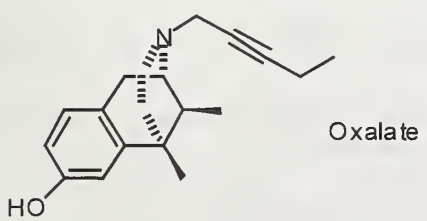


Fig NIH 11254-PPt-W- Results of a study in which single doses of NIH 11254 were given to morphine-dependent monkeys.

Comment: The results indicate that NIH 11254 has opioid antagonist properties.

NIH 11255 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan·oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 1.65 (0.52 – 5.21)
3) **PPQ** – 23% at 1, 38% at 10 and 28% at 30
4) **HP** – 31% at 1, 25% at 10 and inactive at 30

MONKEY DATA – PPt-W

As illustrated in the figure, NIH 11255 precipitated withdrawal in morphine-dependent monkeys. Potency estimate is 1/100 that of naloxone hydrochloride, the reference standard. Duration of action is at least as long as that of the reference standard.

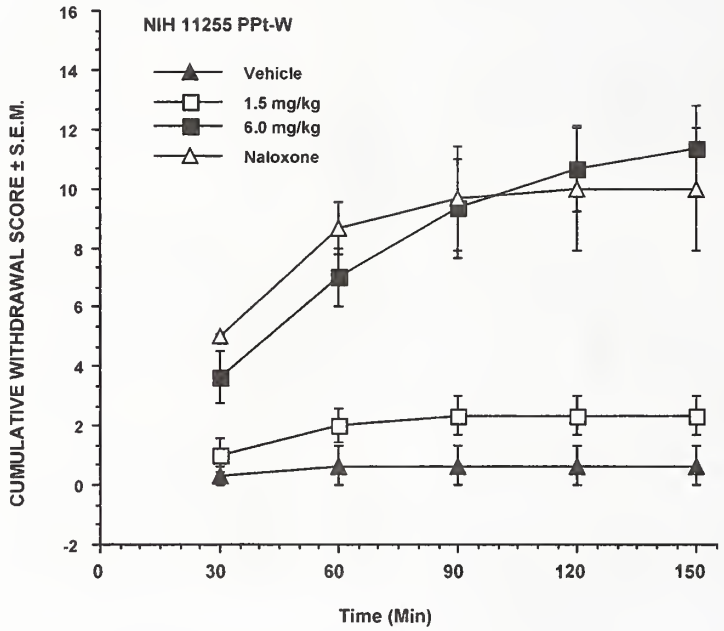
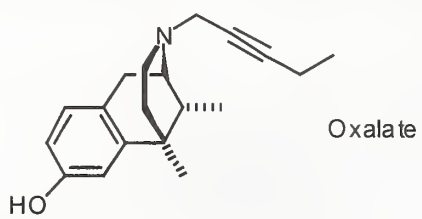


Fig NIH 11255-PPt-W. Results of a study in which single doses of NIH 11255 were given to morphine-dependent monkeys.

Comment: NIH 11255 is a weak opioid antagonist in mice and rhesus monkeys

NIH 11256 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan·oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

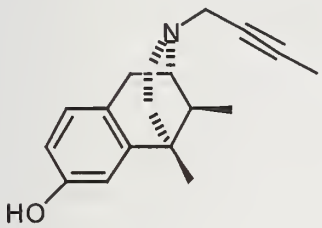
1) **TF** – Inactive at 1, 48% at 3, 39% at 10 and 49% at 30
2) **TF vs. M** – 4.7 (1.2 – 18.3)
3) **PPQ** – 0.57 (0.34 – 0.96)
4) **HP** – 14% at 1, 46% at 10 and 29% at 30

MONKEY DATA - SDS

At doses of 1.5 and 6 mg/kg (n = 2 per dose), NIH 11256 produced a non dose related attenuation of withdrawal signs. However, drug supply precluded a full evaluation.

Comment: In the mouse, NIH 11256 appeared to be a weak mu-opioid receptor antagonist with undefined antinociceptive properties. The results obtained in the monkey assay were inconclusive.

NIH 11257 (+)-(1S,5S,9S)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·oxalate



Oxalate

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1 and 10, 13% at 30
2) **TF vs. M** – 13.2 (4.5 – 38.2)
3) **PPQ** – Inactive at 1, 10 and 30
4) **HP** – 11% at 1, 10% at 10 and 27% at 30

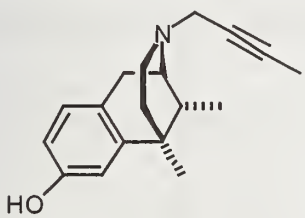
Ataxia noted at 30 in TF test.

MONKEY DATA – PPt-W

At 1 and 4 mg/kg (n = 2/dose), NIH 11257 precipitated withdrawal in morphine-dependent monkeys. The drug was much less potent than naloxone hydrochloride and had a similar duration of action.

Comment: NIH 11257 has rather weak opioid-antagonist properties in the mouse and in the monkey.

NIH 11258 (-)-(1R,5R,9R)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·oxalate



Oxalate

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 33% at 1, 4% at 10 and 30
2) **TF vs. M** – 0.65 (0.15 – 2.75)
3) **PPQ** – 0.21 (0.12 – 0.34)
4) **HP** – 25% at 1, inactive at 10 and 30

Straub tail and mild ataxia noted at 10 and 30 mg/kg in HP test.

MONKEY DATA – SDS

As shown in the accompanying figure, NIH 11258, at doses of 1 and 4 mg/kg, precipitated withdrawal in morphine-dependent monkeys. Duration of action was similar to that of naloxone hydrochloride. Potency estimate is 1/10 that of naloxone hydrochloride.

NIH 11258 (continued)

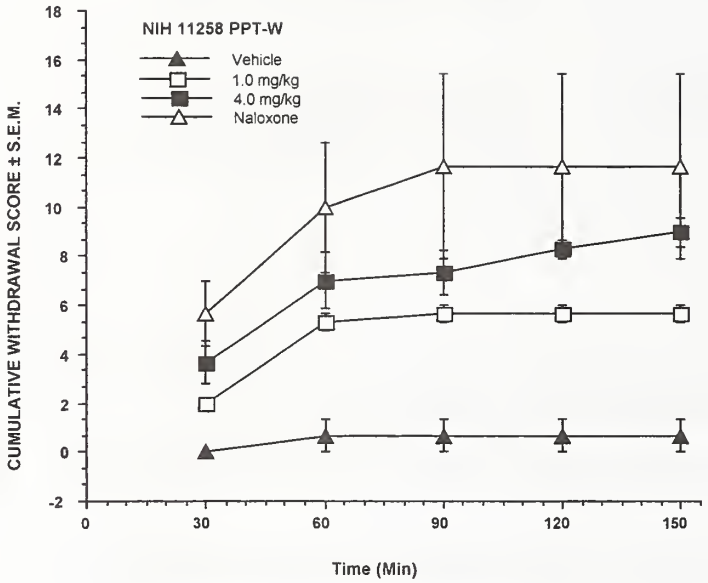
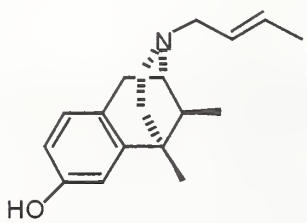


Fig NIH 11258-PPt-W- Results of a study in which single doses of NIH 11258 were given to morphine-dependent monkeys.

Comment: The profile of activity in the mouse and monkey indicates that NIH 11258 is an opioid antagonist with uncharacterized analgesic activity.

NIH 11259 (+)-(1S,5S,9S)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·oxalate



Oxalate

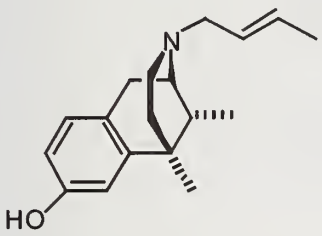
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 12% at 1, inactive at 10 and 36% at 30
3) **PPQ** – 20% at 1, inactive at 10 and 27% at 30
4) **HP** – Inactive at 1, 10 and 30

Ataxia and Straub tails noted at the high dose.

Comment: This compound does not display remarkable opioid activity.

NIH 11260 (-)-(1R,5R,9R)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·oxalate



Oxalate

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 0.32 (0.24 – 0.43)
3) **PPQ** – 16% at 0.3, 48% at 1, 57% at 3, 45% 59% at 30
4) **HP** – 31% at 1, 5% at 10 and inactive at 30

MONKEY DATA – PPt-W

NIH 11260 was tested at 1 and 4 mg/kg. It produced a dose-related increase in the number of withdrawal signs. Potency is estimated as 1/10 that of naloxone hydrochloride. Duration of action was at least that of the reference standard.

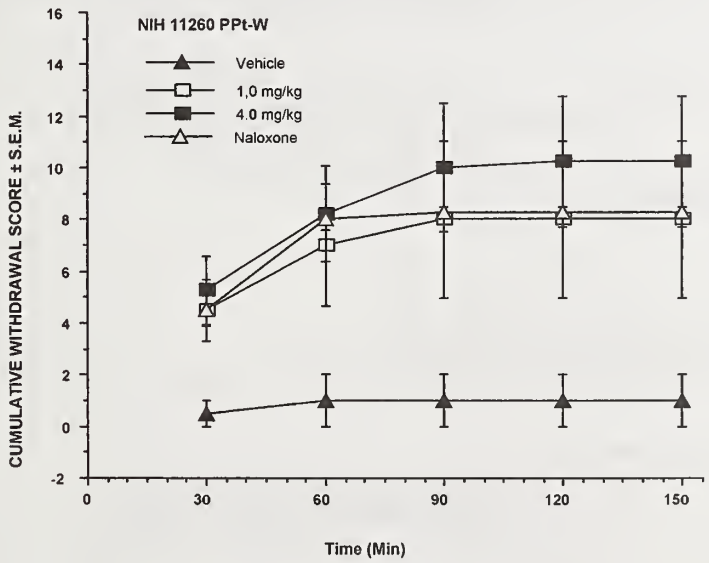
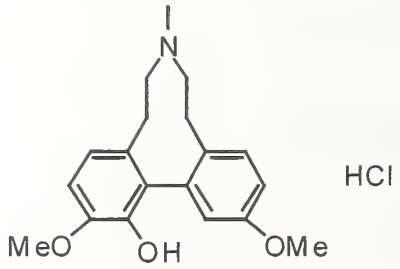


Fig NIH 11260-PPt-W- Results of a study in which single doses of NIH 11260 were given to morphine-dependent monkeys.

Comment: The results in mice and morphine-dependent monkeys indicate that NIH 11260 is an opioid antagonist.

NIH 11261 (+)-Neodihydrothebaine.HCl



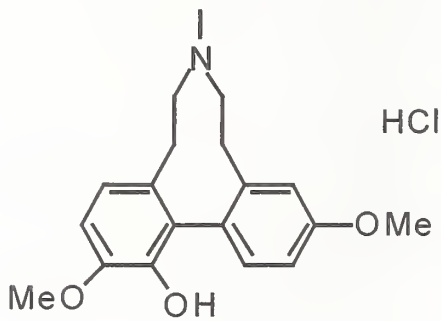
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 4.59 (1.79 – 11.79)
4) **HP** – 19% at 1 and 23% at 10

Limited drug supply precluded further testing.

Comment: The results indicate weak antinociceptive activity in the mouse.

NIH 11262 (+)-Bractazonine.HCl

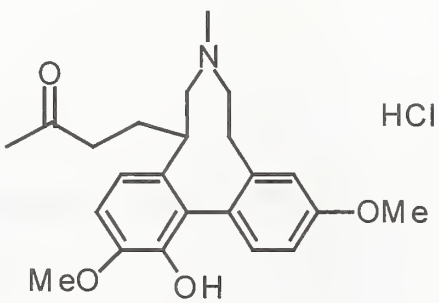


MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 24% at 1 and inactive at 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 13% at 1 and inactive at 10
4) **HP** – Inactive at 1 and 10

Comment: In the mouse, NIH 11262 is devoid of antinociceptive activity.

NIH 11263 (+)-(3-Oxobutyl)bractazonine.HCl



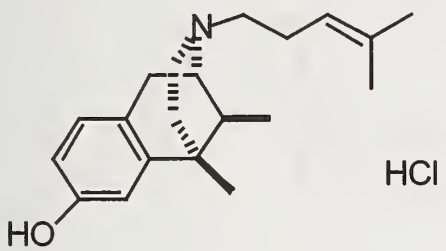
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 30% at 1 and inactive at 10
4) **HP**– Inactive at 1 and 10% at 10

Limited supplies precluded further testing. Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in water.

Comment: As tested, NIH 11263 is inactive regarding antinociceptive opioid agonist or antagonist properties.

NIH 11265 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan·HCl



MOUSE DATA – ED50 OR AD50
(95 % C.L.) (μg/brain or % change)

1) **TF** – Inactive at 1, 13% at 10 and 51% at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – Inactive at 1, 10 and 30
4) **HP** – 7.33 (3.56 – 15.04)

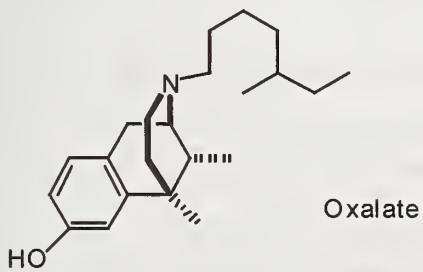
Vehicle was 5% hydroxypropyl-beta-cyclodextrin in sterile water for injection.

MONKEY DATA - SDS

Because of limited supplies, only 2 monkeys per dose (3 and 12 mg/kg) could be tested. The available data suggested that NIH 11265 exacerbated withdrawal.

Comment: It is unusual for a compound to show more activity in the HP test than in the TF test. Furthermore, the mouse and monkey data are not complementary regarding opioid activity. NIH 11265 may have unremarkable opioid properties.

NIH 11266 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan·oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 24.35 (10.21 – 50.10)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 6.31 (2.69 – 14.78)
4) **HP** – 44% at 1, 45% at 10 and 64% at 30

Vehicle was 5% Hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA – SDS

At doses of 4.5 and 18 mg/kg, NIH 11266 did not substitute for morphine or exacerbate withdrawal. Morphine sulfate, the positive control, completely suppressed withdrawal signs (see accompanying illustration). Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in sterile water.

NIH 11266 (continued)

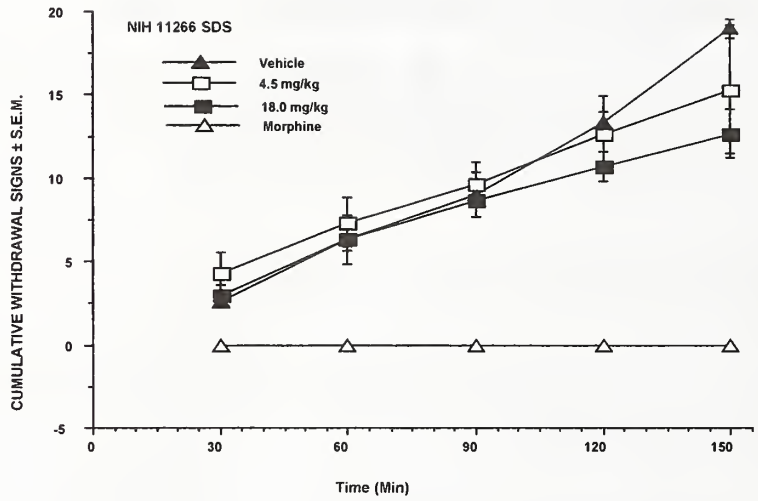
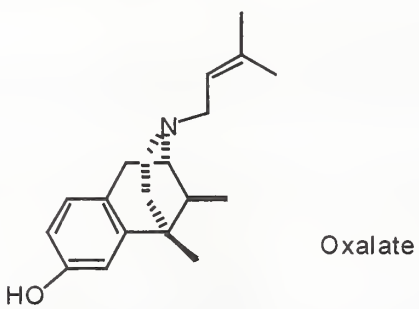


Fig NIH 11266 SDS - Results of study in which single doses of NIH 11266 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The antinociceptive profile of activity in the mouse is typical of that of a mu-and/or kappa-opioid agonist. In the morphine dependent monkey, NIH 11266 appeared to be inactive.

NIH 11269 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan·oxalate



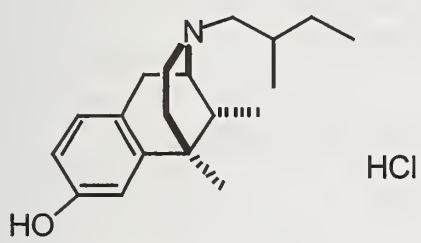
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c).

1) **TF** – Inactive at 1 and10 and 6% at 30
2) **TF vs. M** – 9% at 1, inactive at 10 and 15% at 30
3) **PPQ** – 14% at 1, 35% at 10 and 30
4) **HP** – 11% at 1, 18% at 10 and inactive at 30

Vehicle was 5% Hydroxypropyl-beta-cyclodextrin.

Comment: The results in mice are not indicative of opioid antinociceptive agonist or antagonist activity.

NIH 11270 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 1.98 (1.14 – 3.45)
2) **TF vs. M** – 25% at 1, Inactive at 10 and 4% at 30
3) **PPQ** – 0.79 (0.51 – 1.11)
4) **HP** – 42% at 1, 46% at 3, 64% at 10 and 62% at 30

Straub tail and ataxia were noted. Vehicle was 5% hydroxypropyl-beta- cyclodextrin in water for injection.

MONKEY DATA – SDS

At 0.5 and 2.5 mg/kg, NIH 11270 attenuated withdrawal scores as shown in the accompanying figure. Signs designated as jaw sag, slowing and ataxia were noted at the higher dose and slowing and eyelid ptosis were seen at the lower dose. The combination of low vehicle scores and ambiguous responses to the sign designated abdominal palpation complicate the interpretation of results. NIH 11270 may have mu-opioid activity and also display other CNS properties.

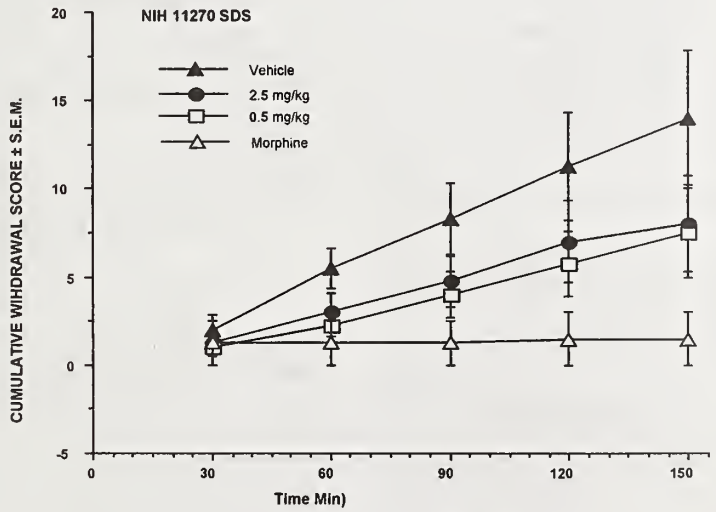
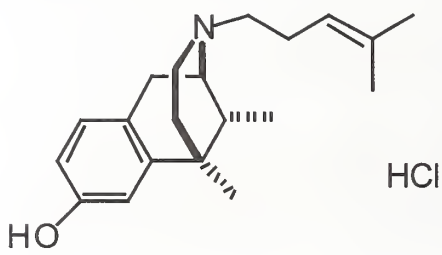


Fig. NIH 11270-SDS- Results of study in which single doses of NIH 11270 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: Overall, the data suggests mu-opioid agonist activity and/or other CNS effects.

NIH 11272 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – 0.25 (0.18 – 0.35)
2) **TF vs. M** – Inactive at 1, 10% at 10 and 2% at 30
3) **PPQ** – 0.054 (0.02 – 0.09)
4) **HP** – 0.11 (0.06 – 0.20)

Straub tail noted in TF and TF vs M tests. Vehicle was 5% hydroxypropyl-beta- cyclodextrin.

MONKEY DATA –SDS

As illustrated in the figure, NIH 11272 substituted completely for morphine at the higher dose. Duration of action appeared to be shorter than that of the morphine control.

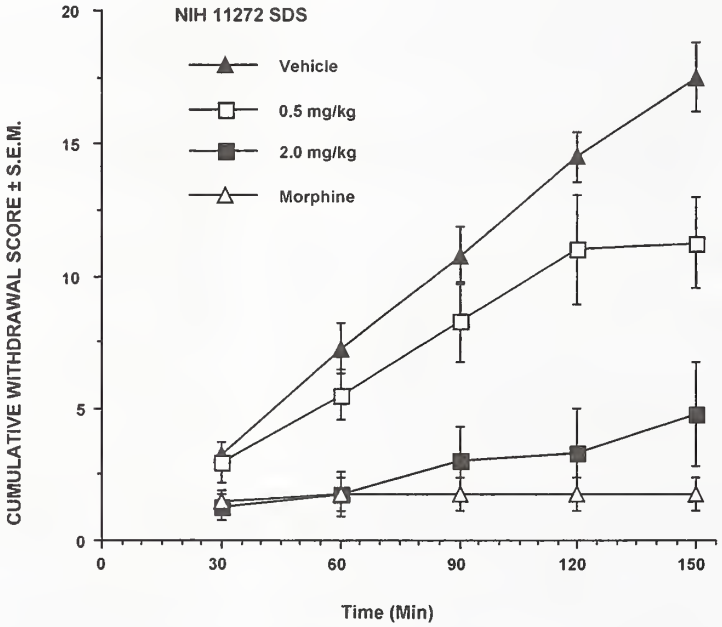
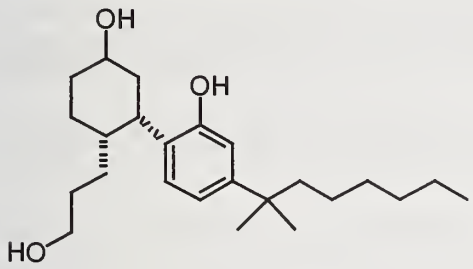


Fig. NIH 11272-SDS- Results of study in which single doses of NIH 11272 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This profile of activity is that of a classical mu-opioid agonist.

FNIH 11276 (CP 55940) (1R,3R,4R)-3-[2-hydroxy-4-(1, 1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)-cyclohexan-1-ol)



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Not tested
2) **TF vs. M** – Not Tested
3) **PPQ** – 0.0095 (0.0058 – 0.0157
4) **HP** – Not tested

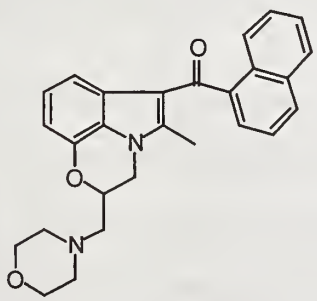
Vehicle was emulphor:ethanol:saline (1:1:18)

Table 1. Effects of CB1 and CB2 antagonists versus a classical cannabinoid agonist

AD50 or Percent Effect versus ED80 of NIH 11276 in the PPQ test mg/kg s.c.	
SR 141716A (CB1 antagonist)	1.04 (0.224 – 4.869)
SR 144528 (CB2 antagonist)	Inactive at 1 and 10

Comment: The results indicate that NIH 11276 has prominent CNS cannabinoid CB1 activity.

NIH 11277 (Win 55,212-2) (R)-(+)-[2,3-Dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-6yl](1-napthalenyl)methanone



MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** – Not tested
2) **TF vs. M** – Not tested
3) **PPQ** – 0.17 (0.08 – 0.33)
4) **HP** –Not tested

Vehicle was emulphor:ethanol:saline (1:1:18).

Effects of CB1 and CB2 antagonists versus a cannabinoid agonist (Win 55,212-2)

AD50 or Percent Effect versus ED80 of NIH11277 in the PPQ test mg/kg s.c.	
SR 141716A (CB1 antagonist)	0.1 (0.046 – 0.217)
SR 144528 (CB2 antagonist)	Inactive at 1 and 10

Comment: The results indicate that NIH 11277 has significant central cannabinoid CB1 activity.

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AUTHOR INDEX

SUBJECT INDEX

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